

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
27 May 2004 (27.05.2004)

PCT

(10) International Publication Number
WO 2004/043300 A1

(51) International Patent Classification⁷: **A61F 2/06**

(21) International Application Number:
PCT/US2003/035627

(22) International Filing Date:
7 November 2003 (07.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/424,577 7 November 2002 (07.11.2002) US
60/424,607 7 November 2002 (07.11.2002) US
60/424,574 7 November 2002 (07.11.2002) US
60/424,576 7 November 2002 (07.11.2002) US
60/424,575 7 November 2002 (07.11.2002) US

(71) Applicant (for all designated States except US): **ABBOTT LABORATORIES** [US/US]; D-377 AP6A-1, 100 Abbott Park Road, Abbott Park, IL 60064-6008 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **VERLEE, Donald** [US/US]; 1109 Pine Tree LN, Libertyville, IL 60048 (US).

CROMACK, Keith [US/US]; 18066 W. Banbury Drive, Gurnee, IL 60031 (US). **TARCHA, Peter** [US/US]; 21651 Gelden Road, Lake Villa, IL 60046 (US). **TONER, John** [US/US]; 817 Fair Way, Libertyville, IL 60048 (US). **HUL, Ho-Wa** [US/US]; 1116 Ashbury Lane, Residence:, Libertyville, IL 60048 (US).

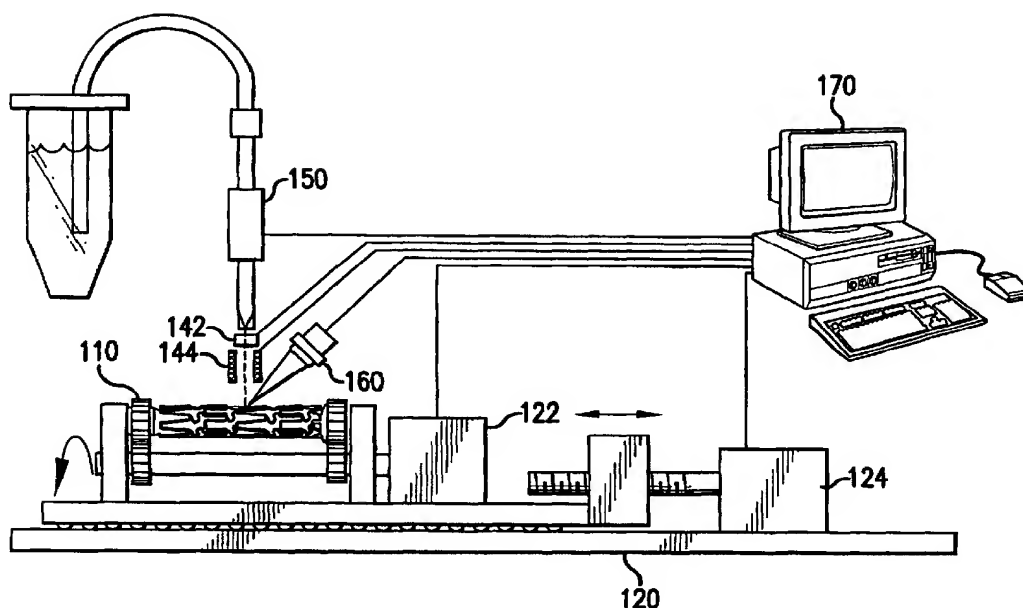
(74) Agents: **WARK, Allen, W.** et al.; Dept 377/AP6A-1, 100 Abbott Park Road, Abbott Park, IL 60064-6008 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,

[Continued on next page]

(54) Title: PROSTHESIS WITH MULTIPLE DRUGS IN DISCRETE UNMIXED DROPLETS



(57) Abstract: An interventional device for delivery of multiple beneficial agents. The device includes a prosthesis having a surface loaded with a plurality of discrete droplets of first and second beneficial agents. The discrete droplets of beneficial agent are loaded along a first controlled trajectory and the second beneficial agent is loaded along a second controlled trajectory. The first controlled trajectory and the second controlled trajectory can be aligned to allow mixing of the first and second beneficial agents prior to being loaded onto the surface of the prosthesis.

WO 2004/043300 A1



SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

PROSTHESIS WITH MULTIPLE DRUGS IN DISCRETE UNMIXED DROPLETS

BACKGROUND OF THE INVENTION

5

Field of the Invention

The present invention relates to an interventional device including a prosthesis loaded with a plurality of discrete droplets of a first beneficial and of a second beneficial agent. The invention also relates to an interventional device having a first surface that is loaded with a first beneficial agent, and a second surface loaded with a second beneficial agent. The invention also relates to a method of loading multiple beneficial agents onto first and second surfaces of a prosthesis, and to a method of manufacturing an interventional device for the delivery of a first beneficial agent and a second beneficial agent from separate surfaces.

15

Description of Related Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. This procedure generally entails introducing a catheter assembly into the cardiovascular system of a patient via the brachial or femoral artery, and advancing the catheter assembly through the coronary vasculature until a balloon portion thereon is positioned across an occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress against the atherosclerotic plaque of the lesion to remodel the vessel wall. Subsequently, the balloon is deflated to allow the catheter assembly to be withdrawn from the vasculature.

While PCTA is widely used, it suffers from two unique problems. First, the blood vessel may suffer acute occlusion immediately after or within the initial hours after the dilation procedure. Such occlusion is referred to as "abrupt closure." Abrupt closure occurs in approximately five percent of cases in which PTCA is employed. The primary mechanisms of abrupt closures are believed to be elastic recoil, arterial dissection and/or thrombosis. The second problem associated with this procedure is the re-narrowing of an artery after an initially successful angioplasty. This re-narrowing is referred to as "restenosis," which among other things, typically occurs within the first six months after

angioplasty. Restenosis is believed to be due to the proliferation and migration of cellular components from the arterial wall, as well as through geometric changes in the arterial wall referred to as "remodeling."

To reduce occlusion of the artery, and the development of thrombosis and/or
5 restenosis, an expandable interventional device or prosthesis, one example of which includes a stent, is implanted in the lumen to maintain the vascular patency. Additionally, to better effectuate the treatment of such vascular disease, it is preferable to load an intraluminal device or prosthesis with one or more beneficial agents, such as antiproliferatives, for delivery to a lumen. One commonly applied technique for the local delivery of a drug is
10 through the use of a polymeric carrier coated onto the surface of a stent, as disclosed in Berg et al., U.S. Pat. No. 5,464,650, the disclosure of which is incorporated herein by reference. Such conventional methods and products generally have been considered satisfactory for their intended purpose. However, some problems associated with such drug eluting interventional devices is the variability in drug loading across an interventional device, as
15 well as the variability in drug concentration from device to device. Other disadvantages include the inability to tightly control and maintain drug concentration, the inability to verify drug distribution or drug loading on any given device, the inability to vary drug distribution in a controlled and predetermined manner to effect a more desirable drug loading profile, the inability to load different, and in particular incompatible or reactive drugs onto the same
20 surface of a device, and the difficulty in controlling the local areal density of beneficial agent that is delivered to the lumen, particularly if the interventional device is an overlapping or bifurcated device coated with beneficial agent.

As evident from the related art, conventional methods of loading interventional devices with beneficial agents, such as drugs, often requires coating the entire prosthesis
25 with a polymer capable of releasing therapeutic drugs, as disclosed in Campbell, U.S. 5,649,977 and Dinh et al., U.S. Patent No. 5,591,227, the disclosures of which are incorporated by reference. Because certain interventional devices may have a varied surface area along its length, such conventional loading techniques results in unintentional or undesirable dosage variations. Additionally, if it is desired to superimpose two or more
30 conventionally-loaded prostheses, such as with nested stents or bifurcated stents, the total dosage of beneficial agent to the lumen will exceed the nominal or desired dosage. Another drawback of the conventional methods of loading interventional devices with beneficial

agents is the lack of selective dosing, such as providing various beneficial agents or various concentrations of the same beneficial agent at different locations on a prosthesis to effect a therapy at specific targeted sites.

Thus, there remains a need for efficient and economic methods for controlling the
5 loading of beneficial agent onto a prosthesis so as to provide an interventional device having a varied distribution profile of beneficial agent to effect therapy at targeted locations of the lumen. Additionally, there is a need for an interventional device capable of providing combination therapy of two or more beneficial agents loaded on different surfaces of a prosthesis to effectuate systemic release as well as release to the wall of the lumen. Further, a
10 need exists for the loading of incompatible beneficial agents onto the same surface of a prosthesis. The advantages of the present invention satisfy the aforementioned needs.

SUMMARY OF THE INVENTION

The purpose and advantages of the present invention will be set forth in and will
15 become apparent from the description that follows, as well as will be learned by practice of the invention.

Additional advantages of the invention will be realized and attained by the methods and systems particularly pointed out in the written description and claims hereof, as well as from the appended drawings.

20 To achieve these and other advantages and in accordance with the purpose of the invention, as embodied and broadly described, the invention includes an interventional device for the delivery of multiple beneficial agents wherein the device comprises a prosthesis to be deployed in a lumen, the prosthesis having a surface; a plurality of discrete droplets of a first beneficial agent loaded on the surface of the prosthesis; and a plurality of discrete droplets of
25 a second beneficial agent loaded on the surface of the prosthesis.

In a further aspect of the invention, the first beneficial agent and the second beneficial agent can be incompatible with each other or detrimental to each other. The first beneficial agent can be dissolved in a first solvent and the second beneficial agent can be dissolved in a second solvent, wherein the first solvent and the second solvent are immiscible. Similarly,
30 the first beneficial agent can react with the second beneficial agent. It is possible for the first beneficial agent to be more hydrophobic than the second beneficial agent. Also, the discrete droplets of the first beneficial agent can be loaded along a first controlled trajectory and the

discrete droplets of the second beneficial agent can be loaded along a second controlled trajectory, wherein the first controlled trajectory and the second controlled trajectory are aligned to allow the first beneficial agent and the second beneficial agent to mix prior to being loaded onto the surface of the prosthesis.

5 In a still further aspect of the invention, the discrete droplets of the first beneficial agent and of the second beneficial agent can mix on the surface of the prosthesis. The first beneficial agent can be dissolved in a solvent wherein the second beneficial agent causes the first beneficial agent to precipitate out of the solvent. Also, the first beneficial agent can be mixed with a binder, wherein the second beneficial agent cures the binder. The first
10 beneficial agent and the second beneficial agent also can be loaded on the prosthesis in unmixed droplets to provide an interspersed pattern of the first beneficial agent and the second beneficial agent. The invention also contemplates an interventional device wherein the first beneficial agent and the second beneficial agent are loaded on the prosthesis in unmixed droplets to provide an overlapping pattern of the first beneficial agent and the
15 second beneficial agent.

 In a further aspect of the invention, an interventional device is provided wherein at least one of the first beneficial agent and the second beneficial agent is mixed with a binder prior to being loaded on the prosthesis. Preferably, the second beneficial agent cures the binder on the prosthesis with the first beneficial agent mixed therein.

20 In accordance with another aspect of the invention, an interventional device is provided wherein the first beneficial agent is mixed with a binder having a first release rate for delivery of the first beneficial agent. The second beneficial agent can be mixed with a binder having a second release rate for delivery of the second beneficial agent; the first release rate being different than the second release rate. The first beneficial agent can be
25 different than the second beneficial agent.

 In accordance with another aspect of the invention, an interventional device is provided wherein the first beneficial agent has a first local areal density and the second beneficial agent has a second local areal density. At least one of the first local areal density and the second local areal density can be uniform across a selected portion of the prosthesis.
30 Also, at least one of the first local areal density of beneficial agent and the second local areal density can be varied across a selected portion of the prosthesis. The first local areal density of the first beneficial agent can be different than the second local areal density of the second

beneficial agent. The interventional device can further include a third beneficial agent loaded on at least one of the first surface and second surface of the prosthesis.

In accordance with still another aspect of the invention, an interventional device is provided wherein the prosthesis further includes a layer of base material on a selected portion thereof, and the first beneficial agent and the second beneficial agent are loaded to the base material layer in unmixed droplets. The base material layer defines a pattern for loading the first beneficial agent and the second beneficial agent.

In accordance with a further aspect of the invention, the prosthesis includes at least one cavity defined therein. The cavity can be filled with multiple beneficial agents.

Preferably, the at least one cavity is at least partially loaded with a base material, and the first beneficial agent and the second beneficial agent are loaded to the base material.

The invention also provides a method of loading multiple beneficial agents onto a prosthesis for delivery within a lumen wherein the method comprises the steps of providing a prosthesis to be deployed within a lumen; providing a first beneficial agent to be loaded on the prosthesis; providing a second beneficial agent to be loaded on the prosthesis; dispensing the first beneficial agent and the second beneficial agent in discrete droplets onto the prosthesis; each droplet having a controlled trajectory.

In accordance with a further aspect of the invention, the first beneficial agent provided by the first beneficial agent providing step is incompatible with the second beneficial agent provided by the second beneficial agent providing step. The first beneficial agent provided by the first beneficial agent providing step can be dissolved in a first solvent and the second beneficial agent provided by the second beneficial agent providing step can be dissolved in a second solvent. The first solvent and the second solvent can be immiscible. The first beneficial agent provided by the first beneficial agent providing step also can be reactive with the second beneficial agent provided by the second beneficial agent providing step. The first beneficial agent provided by the first beneficial agent providing step can react with the second beneficial agent provided by the second beneficial agent providing step to form a third beneficial agent onto the prosthesis. Furthermore, the dispensing steps can be performed to define an interspersed pattern of the first beneficial agent droplets and the second beneficial agent droplets on the prosthesis, if desired. The dispensing steps are performed simultaneously. The dispensing steps also can be performed to define an overlapping pattern of the first beneficial agent and the second beneficial agent.

In accordance with another aspect of the invention, the method can further include the step of mixing the first beneficial agent with a binder prior to the first beneficial agent dispensing step. The second beneficial agent provided by the second beneficial agent providing step cures the binder on the prosthesis with the first beneficial agent mixed therein.

5 In accordance with a still further aspect of the invention, the method can further include the step of mixing the first beneficial agent with a first binder having a first release rate for delivery of the first beneficial agent and the second beneficial agent with a second binder having a second release rate for delivery of the second beneficial agent. The first release rate can be different than the second release rate, and first beneficial agent can be
10 different than the second beneficial agent.

In accordance with another aspect of the invention, a method is provided wherein the first beneficial agent dispensing step is performed to provide the first beneficial agent with a first local areal density and the second beneficial agent dispensing step is performed to provide the second beneficial agent with a second local areal density, wherein at least one of
15 the first local areal density and the second local areal density is varied across a selected portion of the prosthesis.

In accordance with still another aspect of the invention, a method can be provided further including the step of applying a layer of base material on a selected portion of the prosthesis, and the dispensing steps are performed to introduce the first beneficial agent and
20 the second beneficial agent to the base material layer in unmixed droplets. The base material layer can be applied to define a pattern for loading the first beneficial agent and the second beneficial agent.

In accordance with another aspect of the invention, a method is provided wherein the loading steps can include introducing at least one of the first beneficial agent and the second
25 beneficial agent to the base material layer. The base material layer applied by the applying step can define a pattern for loading at least one of the first beneficial agent and second beneficial agent.

The invention also includes an interventional device for delivery of beneficial agent, where the beneficial agent can be selected from a group consisting of antithrombotics,
30 anticoagulants, antiplatelet agents, anti-lipid agents, thrombolytics, antiproliferatives, anti-inflammatories, agents that inhibit hyperplasia, smooth muscle cell inhibitors, antibiotics, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters, antimitotics,

antifibrins, antioxidants, antineoplastics, agents that promote endothelial cell recovery, antiallergic substances, radiopaque agents, viral vectors, antisense compounds, oligonucleotides, cell permeation enhancers, angiogenesis agents, and combinations thereof. The prosthesis can be a stent, graft, stent-graft, filter, or other intravascular device. The
 5 interventional device can include an overcoat applied to at least one of the inner surface or the outer surface of the prosthesis. The fluid-dispenser can be a drop-on-demand fluid type printer or a charge-and-deflect type print head. Furthermore, the beneficial agent can be mixed with a binder and also can be loaded onto the prosthesis with a polymer. The polymer is preferably biodegradable. For example, the polymer can be a macromolecule containing
 10 pendant phosphorylcholine groups such as poly(MPC_w:LMA_x:HPMA_y:TSMA_z), where MPC is 2 methacroyloxyethylphosphorylcholine, LMA is lauryl methacrylate, HPMA is hydroxypropyl methacrylate and TSMA is trimethoxysilylpropyl methacrylate.

In accordance with another aspect of the invention, the beneficial agents can be applied to the interventional device using a fluid jet dispenser capable of dispensing discrete
 15 droplets along a controlled trajectory, such as drop-on-demand fluid type printer or a charge-and-deflect type printer. In accordance with a further aspect of the invention, the beneficial agent can be mixed with a binder. The beneficial agent preferably is loaded onto the prosthesis with a polymer. Preferably, the polymer is a phosphorylcholine material.

In yet another aspect of the invention, the prosthesis has a tubular body when
 20 deployed, wherein the tubular body defines a longitudinal axis. The first surface of the prosthesis is defined as an inner surface of the tubular body, and the second surface of the prosthesis is defined as an outer surface of the tubular body.

In further accordance with the invention, the first surface is loaded with beneficial agent selected from a group consisting of antiplatelet agents, aspirin, cell adhesion promoters,
 25 agents that promote endothelial healing, agents that promote migration and estradiol. The second beneficial agent can be selected from a group consisting of anti-inflammatories, anti-proliferatives, smooth muscle inhibitors, cell adhesion promoters, and the rapamycin analog, ABT-578, i.e., 3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-
 9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-
 30 [(1S,3R,4R)-3-methoxy-4-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-
 6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-

1,5,11,28,29(4H,6H,31H)-pentone;23,27-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

In accordance with another aspect of the invention, an interventional device is provided wherein the first surface of the prosthesis is defined by a plurality of interconnecting structural members and prosthesis includes a first selected set of the structural members and the second surface of the prosthesis includes a second selected set of the structural members. At least one of the first selected set of structural members and the second selected set of structural members can define at least one ring-shaped element extending around a circumference of the tubular body.

In accordance with another aspect of the invention, an interventional device is provided wherein the first beneficial agent has a first local areal density and the second beneficial agent has a second local areal density. At least one of the first local areal density and the second local areal density can be uniform across at least one of the first surface and second surface of the prosthesis. Also, at least one of the first local areal density of beneficial agent and the second local areal density can be varied across at least one of the first surface and second surface of the prosthesis. The first local areal density of the first beneficial agent can be different than the second local areal density of the second beneficial agent. The interventional device can further include an additional beneficial agent loaded on at least one of the first surface and second surface of the prosthesis.

In accordance with another aspect of the invention, an interventional device is provided wherein the prosthesis further includes a layer of a base material on at least a portion of at least one of the first surface and the second surface of the prosthesis. The beneficial agent can be loaded to the base material layer. The base material layer preferably defines a pattern on the prosthesis for loading the beneficial agent.

The invention also provides a method of manufacturing an interventional device for the delivery of beneficial agent wherein the method comprises the steps of providing a prosthesis to be deployed in a lumen, the prosthesis having a first surface and a second surface; providing a first beneficial agent to be delivered from the prosthesis; providing a second beneficial agent to be delivered from the prosthesis; loading the first beneficial agent to at least a portion of the first surface; and loading the second beneficial agent to at least a portion of the second surface. At least one of the first beneficial agent and the second beneficial agent can be loaded by a fluid-dispenser. Preferably, the prosthesis provided by

the prosthesis providing step has a tubular body when deployed, and the first surface of the prosthesis can be defined as an inner surface of the tubular body and the second surface of the prosthesis is defined as an outer surface of the tubular body. The first beneficial agent can be applied to the inner surface of the tubular body by a fluid-dispenser. The first beneficial

5 agent preferably is selected from a group consisting of antiplatelet agents, aspirin, cell adhesion promoters, agents that promote endothelial recovery, agents that promote cell migration agents, angiogenesis agents, and estradiol. The second beneficial agent can be selected from a group consisting of anti-inflammatories, anti-proliferatives, smooth muscle inhibitors, cell adhesion promoters, and the rapamycin analog, ABT-578, i.e.,

10 3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-3-methoxy-4-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone; 23,27-Epoxy-3H-pyrido[2,1-

15 c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

In accordance with another aspect of the invention, a method is provided wherein the first beneficial agent is loaded with a first local areal density by the first beneficial agent loading step, and the second beneficial agent is loaded with a second local areal density by the second beneficial agent loading step. At least one of the first local areal density and the

20 second local areal density can be varied across a selected portion of the prosthesis. The method also can include the steps of providing a third beneficial agent and loading the third beneficial agent on at least one of the first surface and the second surface of the prosthesis. Additionally, the method can further include the step of applying a layer of base material on a selected portion of at least one of the first surface and the second surface.

25 It is to be understood that both the foregoing general description and the following detailed description are exemplary and are intended to provide further explanation of the invention claimed.

The accompanying Figures, which are incorporated in and constitute part of this specification, are included to illustrate and provide a further understanding of the method and

30 system of the invention. Together with the description, the Figures serve to explain the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1a-1c are schematic representations of a prosthesis loaded with beneficial agent having a first portion and a second portion having different local areal densities of beneficial agent in accordance with the present invention, and graphs depicting corresponding areal density.

Figure 2 is a schematic representation of a first prosthesis and a second prosthesis configured to define a nested interventional device, each at least partially loaded with beneficial agent in accordance with the present invention.

Figure 3 is a schematic representation of the first prosthesis and second prosthesis of Figure 2, deployed in overlapping relationship to provide a controlled local areal density across the length of the interventional device.

Figure 4 is a schematic representation of a first prosthesis and second prosthesis configured to define a bifurcated interventional device, each at least partially loaded with beneficial agent in accordance with the present invention.

Figure 5 is a schematic representation of the first prosthesis and second prosthesis of Figure 4, deployed in an overlapping relationship to provide a bifurcated interventional device having a controlled local areal density across a length of the interventional device.

Figure 6 is a schematic representation of an interventional device, and Figure 6a is a detail schematic depicting a raster format for loading beneficial agent thereon.

Figure 7 is a schematic representation of an embodiment of the system of the present invention.

Figures 8a -8d are schematic representations of an “off-axis” dispensing method at various cross-sections of the device of Figure 6.

Figure 9 is a schematic representation of another embodiment of the system of the present invention.

Figure 10 is a schematic representation of discrete droplets loaded in an overlapping manner.

Figure 11 is a schematic representation of a method of loading beneficial agent on an inner surface of an interventional device.

Figure 12 is a schematic representation of the cross-section of the structural element of a prosthesis having a cavity therein.

Figure 13 is a schematic representation of the holding tool assembly of the system of the invention, Figure 13a is a detail schematic depicting the holding tool assembly including the spindle.

5 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reference will now be made in detail to the present preferred embodiments of the method and system for loading beneficial agent onto a prosthesis, and the interventional devices loaded with beneficial agent. Wherever possible, the same reference characters will be used throughout the drawings to refer to the same or like parts.

10 In accordance with the present invention, an interventional device is provided for delivery of beneficial agent within a lumen. Particularly, the present invention is suited for providing an interventional device having a controlled areal density of beneficial agent for the treatment and prevention of vascular or other intraluminal diseases. Generally, "controlled areal density" is understood to mean a known or predetermined amount of
15 beneficial agent, either by weight or volume, over a unit surface area of the interventional device.

As used herein "interventional device" refers broadly to any device suitable for intraluminal delivery or implantation. For purposes of illustration and not limitation, examples of such interventional devices include stents, grafts, stent-grafts, filters, and the
20 like. As is known in the art, such devices may comprise one or more prostheses, each having a first cross-sectional dimension or profile for the purpose of delivery and a second cross-sectional dimension or profile after deployment. Each prosthesis may be deployed by known mechanical techniques such as balloon expansion deployment techniques, or by electrical or thermal actuation, or self-expansion deployment techniques, as well known in the art.
25 Examples of such for purpose of illustration include U.S. Patent No. 4,733,665 to Palmaz; U.S. Patent No. 6,106,548 to Roubin et al.; U.S. Patent No. 4,580,568 to Gianturco; U.S. Patent No. 5,755,771 to Penn et al.; and U.S. Patent No. 6,033,434 to Borghi, all of which are incorporated herein by reference.

For purposes of explanation and illustration, and not limitation, an exemplary
30 embodiment of the interventional device in accordance with the invention is shown schematically in Figure 1a. In accordance with one aspect of the invention, as shown schematically in Figure 1, the interventional device generally includes a prosthesis 10 loaded

with beneficial agent to provide a local areal density of beneficial agent across a length of the interventional device. Particularly, as embodied herein the prosthesis may be a stent, a graft, a stent-graft, a filter, or the like, as previously noted, for intravascular or coronary delivery and/or implantation. However, the prosthesis may be any type of intraluminal member
5 capable of being loaded with beneficial agent.

The prosthesis can be in an expanded or unexpanded state during the loading of beneficial agent. The underlying structure of the prosthesis can be virtually any structural design and the prosthesis can be composed any suitable material such as, but not limited to, stainless steel, "MP35N," "MP20N," elastin (Nitinol), tantalum, nickel-titanium alloy,
10 platinum-iridium alloy, gold, magnesium, polymer, ceramic, tissue, or combinations thereof. "MP35N" and "MP20N" are understood to be trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co., Jenkintown, PA. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium and 10% molybdenum. The
15 prosthesis can be made from bioabsorbable or biostable polymers. In some embodiments, the surface of the prosthesis can include one or more reservoirs or cavities formed therein, as described further below.

The prosthesis can be fabricated utilizing any number of methods known in the art. For example, the prosthesis can be fabricated from a hollow or formed tube that is machined
20 using lasers, electric discharge milling, chemical etching or other known techniques. Alternatively, the prosthesis can be fabricated from a sheet that is rolled into a tubular member, or formed of a wire or filament construction as known in the art.

As noted above, the prosthesis is at least partially loaded with beneficial agent (10a, 10b, 10c). "Beneficial agent" as used herein, refers to any compound, mixture of
25 compounds, or composition of matter consisting of a compound, which produces a beneficial or useful result. The beneficial agent can be a polymer, a marker, such as a radiopaque dye or particles, or can be a drug, including pharmaceutical and therapeutic agents, or an agent including inorganic or organic drugs without limitation. The agent or drug can be in various forms such as uncharged molecules, components of molecular complexes,
30 pharmacologically-acceptable salts such as hydrochloride, hydrobromide, sulfate, laurate, palmitate, phosphate, nitrate, borate, acetate, maleate, tartrate, oleate, and salicylate.

An agent or drug that is water insoluble can be used in a form that is a water-soluble derivative thereof to effectively serve as a solute, and on its release from the device, is converted by enzymes, hydrolyzed by body pH, or metabolic processes to a biologically active form. Additionally, the agents or drug formulations can have various known forms
 5 such as solutions, dispersions, pastes, particles, granules, emulsions, suspensions and powders. The drug or agent may or may not be mixed with polymer or a solvent as desired.

For purposes of illustration and not limitation, the drug or agent can include antithrombotics, anticoagulants, antiplatelet agents, thrombolytics, antiproliferatives, anti-inflammatory, agents that inhibit hyperplasia, inhibitors of smooth muscle proliferation,
 10 antibiotics, growth factor inhibitors, or cell adhesion inhibitors. Other drugs or agents include but are not limited to antineoplastics, antimitotics, antifibrins, antioxidants, agents that promote endothelial cell recovery, antiallergic substances, radiopaque agents, viral vectors, antisense compounds, oligonucleotides, cell permeation enhancers, angiogenesis agents, and combinations thereof.

15 Examples of such antithrombotics, anticoagulants, antiplatelet agents, and thrombolytics include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapriprost, prostacyclin and prostacylin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa (platelet membrane receptor antagonist antibody), recombinant hirudin, and thrombin inhibitors such
 20 as Angiomax™, from Biogen, Inc., Cambridge, Mass; and thrombolytic agents, such as urokinase, e.g., Abbokinase™ from Abbott Laboratories Inc., North Chicago, IL, recombinant urokinase and pro-urokinase from Abbott Laboratories Inc., tissue plasminogen activator (Alteplase™ from Genentech, South San Francisco, CA and tenecteplase (TNK-tPA).

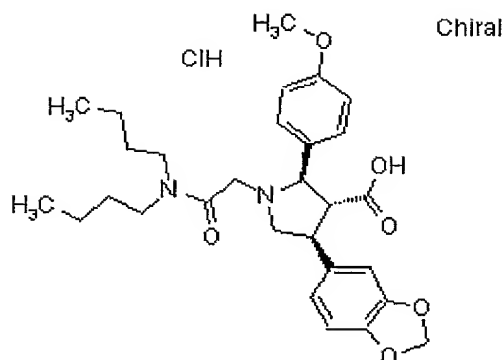
25 Examples of such cytostatic or antiproliferative agents include rapamycin and its analogs such as everolimus, ABT-578, i.e.,
 3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-
 9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-
 [(1S,3R,4R)-3-methoxy-4-tetrazol-1-yl]cyclohexyl]-1-methylethyl]-10,21-dimethoxy-
 30 6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-
 1,5,11,28,29(4H,6H,31H)-pentone;23,27-Epoxy-3H pyrido[2,1-
 c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone, which is disclosed in

US Patent No. 6,015,815, US Patent No. 6,329,386, US Publication 2003/129215, filed on September 6, 2002, and US Publication 2002/123505, filed September 10, 2001, the disclosures of which are each incorporated herein by reference thereto, tacrolimus and pimecrolimus, angiopeptin, angiotensin converting enzyme inhibitors such as captopril, e.g., 5 Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, Conn., cilazapril or lisinopril, e.g., Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, NJ; calcium channel blockers such as nifedipine, amlodipine, cilnidipine, lercanidipine, benidipine, trifluperazine, diltiazem and verapamil, fibroblast growth factor antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin, e.g. Mevacor® from Merck & Co., 10 Inc., Whitehouse Station, NJ. In addition, topoisomerase inhibitors such as etoposide and topotecan, as well as antiestrogens such as tamoxifen may be used.

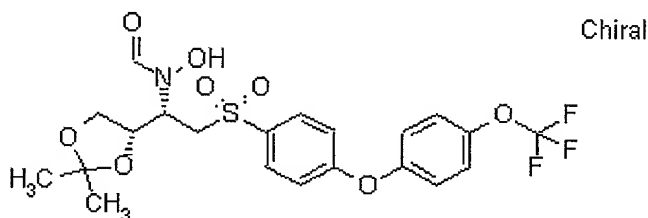
Examples of such anti-inflammatories include colchicine and glucocorticoids such as betamethasone, cortisone, dexamethasone, budesonide, prednisolone, methylprednisolone and hydrocortisone. Non-steroidal anti-inflammatory agents include flurbiprofen, ibuprofen, 15 ketoprofen, fenoprofen, naproxen, diclofenac, diflunisal, acetaminophen, indomethacin, sulindac, etodolac, diclofenac, ketorolac, meclofenamic acid, piroxicam and phenylbutazone.

Examples of such antineoplastics include alkylating agents such as altretamine, bendamucine, carboplatin, carmustine, cisplatin, cyclophosphamide, fotemustine, ifosfamide, lomustine, nimustine, prednimustine, and treosulfine, antimitotics such as vincristine, 20 vinblastine, paclitaxel, e.g., TAXOL® by Bristol-Myers Squibb Co., Stamford, Conn., docetaxel, e.g., Taxotere® from Aventis S.A., Frankfurt, Germany, antimetabolites such as methotrexate, mercaptopurine, pentostatin, trimetrexate, gemcitabine, azathioprine, and fluorouracil, and antibiotics such as doxorubicin hydrochloride, e.g., Adriamycin® from Pharmacia & Upjohn, Peapack, NJ, and mitomycin, e.g., Mutamycin® from Bristol-Myers 25 Squibb Co., Stamford, Conn, agents that promote endothelial cell recovery such as Estradiol.

Additional drugs which may be utilized in this application include dexamethasone; fenofibrate; inhibitors of tyrosine kinase such as RPR-101511A; PPAR-alpha agonists such as Tricor™ formulation from Abbott Laboratories Inc., North Chicago, IL; endothelin receptor antagonists such as ABT-627 having general formula $C_{29}H_{38}N_2O_6.ClH$, and the 30 following structural formula



from Abbott Laboratories Inc., North Chicago, IL, as disclosed in US Patent No. 5,767,144, the disclosure of which is incorporated herein by reference; matrix metalloproteinase inhibitors such as ABT-518 {[S - (R*,R*)]-N-[1-(2,2-dimethyl-1,3-dioxol-4-yl)-2-[[4-[4-(trifluoro-methoxy)-phenoxy]phenyl]sulfonyl]ethyl]-N-hydroxyformamide }
 5 having general formula C₂₁H₂₂F₃NO₈S and having the following structural formula



from Abbott Laboratories Inc., North Chicago, IL, which is disclosed in U.S. Patent No. 6,235,786, the disclosure of which is incorporated herein by reference; ABT 620 {1-Methyl-N-(3,4,5-trimethoxyphenyl)-1H-indole-5-sulfonamide}, which is disclosed in US Patent No. 6,521,658, the disclosure of which is incorporated herein by reference; antiallergic agents such as permirolast potassium nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine,
 15 and nitric oxide.

While the foregoing beneficial agents are known for their preventive and treatment properties, the substances or agents are provided by way of example and are not meant to be limiting. Further, other beneficial agents that are currently available or may be developed are equally applicable for use with the present invention.

If desired or necessary, the beneficial agent can include a binder to carry, load, or allow sustained release of an agent, such as but not limited to a suitable polymer or similar carrier. The term "polymer" is intended to include a product of a polymerization reaction inclusive of homopolymers, copolymers, terpolymers, etc., whether natural or synthetic, including random, alternating, block, graft, branched, cross-linked, blends, compositions of blends and variations thereof. The polymer may be in true solution, saturated, or suspended as particles or supersaturated in the beneficial agent. The polymer can be biocompatible, or biodegradable.

For purpose of illustration and not limitation, the polymeric material include phosphorylcholine linked macromolecules, such as a macromolecule containing pendant phosphorylcholine groups such as poly(MPC_w:LMA_x:HPMA_y:TSMA_z), where MPC is 2-methacryoyloxyethylphosphorylcholine, LMA is lauryl methacrylate, HPMA is hydroxypropyl methacrylate and TSMA is trimethoxysilylpropyl methacrylate, polycaprolactone, poly-D,L-lactic acid, poly-L-lactic acid, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), polyalkylene oxalates, polyphosphazenes, polyiminocarbonates, and aliphatic polycarbonates, fibrin, fibrinogen, cellulose, starch, collagen, Parylene®, Parylast®, polyurethane including polycarbonate urethanes, polyethylene, polyethylene terephthalate, ethylene vinyl acetate, ethylene vinyl alcohol, silicone including polysiloxanes and substituted polysiloxanes, polyethylene oxide, polybutylene terephthalate-co-PEG, PCL-co-PEG, PLA-co-PEG, polyacrylates, polyvinyl pyrrolidone, polyacrylamide, and combinations thereof. Non-limiting examples of other suitable polymers include thermoplastic elastomers in general, polyolefin elastomers, EPDM rubbers and polyamide elastomers, and biostable plastic material such as acrylic polymers, and its derivatives, nylon, polyesters and epoxies. Preferably, the polymer contains pendant phosphoryl groups as disclosed in U.S. Patent Nos. 5,705,583 and 6,090,901 to Bowers et al. and U.S. Patent No. 6,083,257 to Taylor et al., which are all incorporated herein by reference.

The beneficial agent can include a solvent. The solvent can be any single solvent or a combination of solvents. For purpose of illustration and not limitation, examples of suitable solvents include water, aliphatic hydrocarbons, aromatic hydrocarbons, alcohols, ketones,

dimethyl sulfoxide, tetrahydrofuran, dihydrofuran, dimethylacetamide, acetates, and combinations thereof. Preferably, the solvent is ethanol. More preferably, the solvent is isobutanol. Additionally, in another aspect of the invention, multiple beneficial agents are dissolved or dispersed in the same solvent. For purpose of illustration and not for limitation, dexamethasone, estradiol, and paclitaxel are dissolved in isobutanol. Alternatively, dexamethasone, estradiol, and paclitaxel are dissolved in ethanol. In yet another example, dexamethasone, estradiol, and ABT-578, i.e., the rapamycin analog, 3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23-S,26R,27R,34aS)9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-3-methoxy-4-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine -1,5,11,28,29(4H,6H,31H)-pentone; 23,27-Epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone, are dissolved together in one solvent. Preferably, the solvent is ethanol. More preferably, the solvent is isobutanol.

Additionally, the beneficial agent includes any of the aforementioned drugs, agents, polymers, and solvents either alone or in combination.

A number of methods can be used to load the beneficial agent onto the surface of the prosthesis to provide for a controlled local areal density of beneficial agent if performed appropriately. For example, the prosthesis can be constructed to include pores or reservoirs which are impregnated or filled with beneficial agent or multiple beneficial agents. The pores can be sized or spaced apart to correspond to or limit the amount of beneficial agent contained therein in accordance with the desired local areal density pattern along the length of the interventional device, wherein larger pores or more dense spacing would be provided in such portions intended to have a greater local areal density. Alternatively, uniform pores sizes can be provided but the amount of beneficial agent loaded therein is limited accordingly. Additionally, if desired, a membrane of biocompatible material can then be applied over the pores or reservoirs for sustained or controlled release of the beneficial agent from the pores or reservoirs.

According to some of the embodiments, the beneficial agent can be loaded directly onto the prosthesis or alternatively, the beneficial agent is loaded onto a base material layer that is applied to a surface of the prosthesis. For example and not limitation, a base coating, such as a binder or suitable polymer, is applied to a selected surface of the prosthesis such

that a desired pattern is formed on the prosthesis surface. Beneficial agent is then applied directly to the pattern of the base material.

In one aspect of the invention, the desired pattern corresponds to the desired controlled local areal density. For example, a greater amount of base material layer is applied to portions of the interventional device intended to have a greater local areal density of beneficial agent, and a lesser amount of base material is applied to portions of the interventional device intended to have a lower local areal density of beneficial agent.

Alternatively, a suitable base coating capable of retaining beneficial agent therein can be applied uniformly over the surface of the prosthesis, and then selected portions of the base coating can be loaded with the beneficial agent in accordance with the invention. A greater amount of beneficial agent would be loaded over a unit surface area of the base coating intended to have a greater local areal density and a lower amount of beneficial agent would be loaded over a unit surface area intended to have a lower local areal density.

In yet another embodiment of the present invention, the beneficial agent can be applied directly to the surface of the prosthesis. Generally a binder or similar component can be required to ensure sufficient adhesion. For example, this coating technique can include admixing the beneficial agent with a suitable binder or polymer to form a coating mixture, which is then coated onto the surface of the prosthesis. The coating mixture is prepared in higher or lower concentrations of beneficial agent as desired, and then applied to selected portions of the prosthesis appropriately.

In any of the embodiments disclosed herein, a porous or biodegradable membrane or layer made of biocompatible material can be coated over the beneficial agent for sustained release thereof, if desired.

Conventional coating techniques can be utilized to coat the beneficial agent onto the surface of the prosthesis such as spraying, dipping or sputtering and still provide the desired effect if performed appropriately. With such techniques, it may be desirable or necessary to use known masking or extraction techniques to control the location and amount in which beneficial agent is loaded. Prior to coating the prosthesis with beneficial agent, optical machine vision inspection of the prosthesis preferably is utilized to ensure that no mechanical defects exist. Defective prostheses thus can be rejected before wasting beneficial agent, some of which may be very costly.

In accordance with one aspect of the invention, however, the beneficial agent is “printed” onto the surface of the prosthesis by a fluid-dispenser having a dispensing element capable of dispensing beneficial agent in discrete droplets, wherein each droplet has a controlled trajectory. If desired, printing can be combined with conventional coating techniques such as spraying or dipping.

“Fluid-dispenser,” as used herein, refers broadly to any device having a dispensing element capable of dispensing fluid in discrete droplets wherein each droplet has a controlled trajectory. For purposes of illustration and not limitation, examples of such fluid-dispensers include fluid-jetting and similar fluid dispensing technology devices such as a drop-on-demand fluid printer and a charge-and-deflect fluid printer. However, other fluid-dispensers capable of forming a fluid jet or capable of dispensing discrete droplets having a controlled trajectory are within the scope of the present invention. In a preferred embodiment, the fluid-dispenser is a fluid-jet print head. Such equipment is available from MicroFab Technologies of Plano, Texas.

Fluid-jetting and similar technology provides numerous advantages not available with conventional loading techniques. For example, fluid jetting technology can be used to deposit materials, such as chemical reagents, in controlled volumes onto a substrate at a controlled location, as disclosed in U.S. Patent No. 4,877,745 to Hayes et al., incorporated herein by reference.

Fluid jetting can also be used to deposit materials in a reproducible way. Fluid-jet based deposition of materials is data driven, non-contact, and requires no tooling. The “printing” information can be created directly from CAD information and stored digitally in software or hardware. Thus, no masks or screens are required. As an additive process with no chemical waste, fluid-jetting is environmentally friendly. Other advantages include the efficiency of fluid jet printing technology. For example, fluid-jetting can dispense spheres of fluid with diameters of 15 –200 um at rates of 1-25,000 per second for single droplets on demand, and up to 1MHz for continuous droplets. *See* Cooley et al., “Applications of Ink-Jet Printing Technology to BioMEMS and Microfluidic Systems,” *Proc. SPIE Conf. on Microfluidics*, (October 2001), incorporated herein by reference.

In accordance with one aspect of the invention, a method of loading beneficial agent onto a prosthesis for delivery within a lumen is disclosed. The method comprises the steps of providing a prosthesis, beneficial agent to be delivered from the prosthesis, and a fluid-

dispenser having a dispensing element capable of dispensing the beneficial agent in discrete droplets, wherein each droplet has a controlled trajectory. The method further includes creating relative movement between the dispensing element and the prosthesis to define a dispensing path and selectively dispensing the beneficial agent in a raster format to a predetermined portion of the prosthesis along the dispensing path. In particular, the beneficial agent is selectively dispensed from the dispensing element to a predetermined portion of the prosthesis in a raster format along a dispensing path. As used herein "raster format" refers to a continuous or non-continuous dispensing pattern of droplets of beneficial agent dispensed at specific intervals. The relative motion of the dispensing element and the prosthesis to be loaded with beneficial agent creates a dispensing path which includes, for example and as shown in Fig. 6a, a sequential series of linear parallel passes that traverse back and forth along one axis of the prosthesis. The relative motion is continued in a linear manner between forward and backward or right to left and left to right or upward and downward, depending on the frame of reference. A traversal or a pass is completed when the relative motion reverses direction. That is, relative motion continues past the prosthesis, and then decelerates, stops, reverses direction and accelerates to a constant velocity. After each pass, the position of the dispensing element or prosthesis relative to the dispensing element preferably is changed or incremented such that additional droplets do not impact in the same location during the subsequent pass, although a certain degree of overlap may be permitted. For example, as the dispensing element dispenses the beneficial agent along the prosthesis, a fluid dispensing width "w" is defined. The dispensing path defined by the relative movement between the dispensing element and the prosthesis can include a series of parallel passes wherein each parallel pass has a path width no greater than the fluid dispensing width defined by the dispensing element, although a greater path width can be defined if desired.

Alternatively, the dispensing path created by the relative motion of the dispensing element and the prosthesis can include a single continuous helix that wraps continuously around the prosthesis tubular body and along the length of the prosthesis. Fig. 10 schematically depicts such a helical path. In this manner, selectively fluid dispensing in a raster format similar to that of the linear paths previously described can be performed using a helical path if desired. In a preferred embodiment, the direction of travel of relative motion consists of continuously rotating, for example, the prosthesis to be loaded and then

incrementally advancing the dispensing element axially along the prosthesis. Both axial and radial motion preferably begin before the prosthesis 10 is aligned with the dispensing element 150 to receive droplets, so as to enable acceleration of both axes to a constant velocity, and continues beyond the prosthesis where both movements may decelerate, and stop. After each rotation, the position of the dispensing element 150 or of the prosthesis 10 relative to the dispensing element is moved or incremented axially such that additional droplets of beneficial agent preferably do not impact in the same location. Any degree of overlap may be permitted to achieve the desired areal density of beneficial agent.

For purpose of illustration of this method, and as shown in Figs. 6 and 7, the prosthesis 10 includes a plurality of interconnected structural members 12 defining openings 14 therebetween and the beneficial agent 15 is dispensed only when the dispensing element 150 and the structural members 12 within a predetermined portion of the prosthesis 10 are aligned with each other. Accordingly, in this preferred embodiment, dispensing beneficial agent 15 ceases when the dispensing element 150 and the structural members 12 of the prosthesis are not in alignment. To this end, the method can include a detecting step to determine when the dispensing element 150 is aligned with the structural members 12 of a prosthesis 10. The detecting step can be achieved by a sensor 160 such as an optical detector, *e.g.*, linear array detector or infrared detector, ultrasound probe, temperature probe, camera, capacitance meter, electrometer, hall-effect probe, and the like. However, any sensor 160 known in the art for detection is within the scope of the invention. Alternatively, a controller 170 may be provided that is programmed with the structural member locations of a predetermined portion of the prosthesis to be loaded with beneficial agent. In this manner, the dispensing step is performed by the dispensing element as operated by the programmed controller. These aspects of the invention reduce or eliminate webbing and bridging of beneficial agent across openings or gaps within the structure of the prosthesis and minimizes waste. Furthermore, the dispensing element 150 can be aligned such that the controlled trajectory of each droplet is directed normal to the surface of the prosthesis, or at an angle thereto. Similarly, the trajectory path can be aligned to cross the central axis of the prosthesis, or be aligned off-axis thereto.

According to another aspect of the invention, the method of loading beneficial agent onto the prosthesis includes providing a prosthesis including a tubular member having a central axis defined along a length of the tubular member. This method further includes

dispensing beneficial agent from a dispensing element capable of dispensing beneficial agent in discrete droplets and in a controlled trajectory to a surface of the prosthesis, wherein the controlled trajectory of beneficial agent is aligned so as not to intersect the central axis of the tubular member.

5 For example, and for purpose of illustration and not limitation, Figures 8a - 8d depict various cross-sections of the interventional device 10 of Figure 6. In each cross-sectional view, the trajectory path 152 of the discrete droplets 155 is aligned "off-axis" so as not to pass through the central axis 11 of the tubular member. Particularly, and as depicted in Figures 8a through 8d for purpose of illustration and not limitation, the trajectory path 152 of
10 the discrete droplets 155 is aligned tangentially between an inner surface and an outer surface of the tubular wall of the prosthesis 10. In this manner, likelihood of impact of a discrete droplet 155 of beneficial agent 15 with a surface of the prosthesis 10 is enhanced. If desired, however, alternative off-axis trajectory path alignment can be used in accordance with the invention.

15 With reference to Figures 8a - 8d, the prosthesis provided by the prosthesis providing step includes a tubular member having a plurality of interconnected structural members 12 defining openings 14 therebetween, and further wherein the controlled trajectory 152 of each droplet is substantially tangential to a wall or surface of the structural members 12 within the predetermined portion of the prosthesis. In this regard, the controlled trajectory 152 of
20 beneficial agent 15 dispensed from the dispensing element 150 is aligned such that it does not intersect the central axis of the prosthesis. This process allows for greater coverage of the structural elements, without requiring selective operation of the dispensing element, if desired. That is, use of the "off-axis" approach allows for enhanced loading of beneficial agent on the prosthesis without selective or with only limited control of the dispensing
25 element if desired. In a preferred embodiment, however, the dispensing element is at least controlled to terminate dispensing when the trajectory path is not aligned with the solid profile of the predetermined area to be loaded, e.g. axially beyond either end 13 of the prosthesis 10, shown in Fig. 6. In particular, the dispensing element is turned "on" only when the trajectory path of beneficial agent will intersect the solid area swept out by 360 degrees
30 rotation of the prosthesis. The dispensing element is turned off when the trajectory path of beneficial agent would not intersect or will miss the solid area and volume swept out by 360 degrees rotation of the prosthesis.

Alternatively, and in accordance with a preferred embodiment of the invention, the "off-axis" method is performed using the raster technique previously described. That is, with the trajectory path 152 aligned off-axis from the central axis of the prosthesis 10, such as shown in Figure 8a -8d, discrete droplets can be selectively dispensed from the dispensing element 150 only when aligned with a structural member 12 of the prosthesis 10. In this embodiment, the relative motion of the dispensing element 150 and the prosthesis 10 define a dispensing path which includes a sequential series of linear parallel passes that traverse back and forth along one axis of the prosthesis. The relative motion alternates between forward and backward, right to left, left to right, or upward and downward, depending on the frame of reference. A traversal or pass is completed when the relative motion changes direction. That is, relative motion continues past the prosthesis and then decelerates, stops, reversed direction and accelerates to a constant velocity. After each pass, the position of the dispensing element 150 is changed or incremented such that additional drops of beneficial agent do not impact the same location as the previously dispensed droplets during the subsequent pass. Any degree of overlap may be permitted to achieve a desired areal density of beneficial agent.

Alternatively, the relative motion of the dispensing element and the prosthesis define a dispensing path which includes a single continuous helix that wraps around the prosthesis and along its length. The relative motion consists of continuously rotating, for example, the prosthesis and then incrementally advancing the dispensing element 150 axially along the prosthesis. Both axial and radial motion preferably begin before the item is aligned with the dispensing element to receive droplets of beneficial agent, so as to enable acceleration of both axes to a constant velocity, and continues beyond the prosthesis where both movements may decelerate, and stop. After each rotation, the position of the dispensing element or prosthesis relative to the dispensing element is moved or incremented axially such that additional droplets preferably do not impact in the same location. However, any degree of overlap may be permitted to achieve a desired areal density of beneficial agent.

The linear velocity during dispensing of droplets of beneficial agent can be constant or can be varied in a controlled way. Further, the preferable position of the droplet trajectory is such that the droplets interact with the structural surfaces of the prosthesis at or near the tangent to its curved solid surface.

In a preferred embodiment the dispensing path 154 includes a series of parallel passes along a surface of the prosthesis. For example and not limitation, the prosthesis provided can

have a tubular body prior to its deployment in a lumen, and each parallel pass of the dispensing path 154 is parallel to the longitudinal axis 11 of the prosthesis 10 as shown in Fig. 6a. After each pass, the position of the dispensing element 150 or prosthesis 10 is changed or incremented so that the discrete droplets 155 of beneficial agent 15 are dispensed
5 onto a surface of the prosthesis 10 that has not already been loaded. Alternatively, and as previously noted, the parallel passes can define a helical pattern around the longitudinal axis of the stent, wherein each pass is a complete turn of the helical pattern. For purposes of illustration and not limitation, the relative motion of the dispensing element and the prosthesis can include continuously rotating the prosthesis and incrementally advancing the
10 dispensing element axially along the length of the prosthesis. Preferably, after each rotation of the prosthesis, the position of the dispensing element is incrementally changed axially such that additional droplets of beneficial agent that are dispensed from the dispensing element load a surface of the prosthesis not already loaded by a prior pass. In an alternative aspect of the invention, the prosthesis can have a planar body prior loading, such that no rotation of the
15 planar member is required for loading of beneficial agent thereon. The step of dispensing the beneficial agent onto the prosthesis along the dispensing path can be repeated to provide multiple passes along a predetermined portion of the prosthesis.

As noted above, the beneficial agent is selectively dispensed from the dispensing element along the dispensing path in a raster format. In this manner, the raster format can be
20 achieved by turning the dispensing element on and off at predetermined intervals in response to a detector. Alternatively, the beneficial agent can be selectively dispensed in a raster format by programming a controller device that communicates with the dispensing element to dispense the beneficial agent according to the programmed data. A variety of fluid dispensers are available and suitable for providing discrete droplets along a controlled
25 trajectory. For example, a suitable drop-on-demand jetting system can be used, as shown in Figs. 9 and 11, wherein discrete droplets are selectively dispensed from a jetting head. In this manner, the jet stream of discrete droplets can be turned on and off on demand, and the flow rate of discrete droplets can be increased or decreased as desired. Alternatively, if a charge-and-deflect device is used, then a continuous stream of droplets will be generated, and
30 selected droplets will be deflected as is known in the art, such as shown in Fig. 7, as described further below.

In one preferred embodiment of the invention the prosthesis is a stent, and as mentioned above, the fluid-dispenser is a fluid-jetting device. In accordance with the preferred embodiment, a driver 120 continually advances the stent longitudinally along its axis at a constant rate, to define a series of generally parallel passes 154 along the longitudinal axis 11 of the stent 10. The stent is incrementally rotated about its axis at the end of each pass. The stent is rotated at about 1° to about 20° about its longitudinal axis, increments, and preferably is rotated at about 5° increments.

The fluid-jetting head is turned on to provide droplets of beneficial agent whenever a stent strut or structural member is detected immediately in front of the jetting head, or based on a predetermined programmed pattern that corresponds to the stent design, as mentioned above. By further providing controlled flow rate dispensed from the jetting head, the beneficial agent can be provided in a rastered format to confer the stent with a known quantity of beneficial agent. If desired, the known quantity of beneficial agent is dispensed to provide a uniform local areal density based on changes in surface area. As used herein “local areal density” refers to the amount of beneficial agent per unit surface area of the stent or prosthesis.

For example and not limitation, a unit length of two different struts having different strut widths could each be loaded with an equal amount of beneficial agent by adjusting flow rate accordingly. Contrastly, the flow rate of the jetting head can be controlled along the progression of the stent to provide a first portion 10b of the prosthesis 10 with a greater local areal density and a second portion 10a of the prosthesis with a lower local areal density, such as shown in Figure 1. Similarly, the rate of relative movement between the jetting head and the prosthesis can be varied to control local areal density accordingly.

As noted above, the dispensing path 154 is defined by the relative movement between the dispensing element and the prosthesis. The relative movement between the dispensing element and the prosthesis may be performed at a substantially constant velocity, or alternatively at a varied velocity to alter local areal density of beneficial agent, or intermittently. For an example of varied velocity, and with reference to the embodiment of Figure 1a for purpose of illustration and not limitation, the linear travel speed of the prosthesis under the fluid dispenser is performed 50% faster during loading of beneficial agent on the proximal and distal portions 10a and 10c of the prosthesis body to decrease local areal density accordingly. Alternatively, the linear travel speed of the prosthesis under the

fluid dispenser may be 50% slower during loading of beneficial agent on the mid region of the prosthesis body to increase local areal density thereat.

Alternatively, rather than using a raster format, a vector technique can be used wherein a first portion of the stent strut at one end of the stent is positioned in front of the jetting head and the jetting head is turned on. The jetting head is then left on to dispense droplets of beneficial agent at a constant predetermined frequency to provide a predetermined dispensing rate of agent. The two-axis control system, described further below, is directed to continuously move the stent, coordinating both axes simultaneously so that the predetermined shape of the stent struts are advanced in front of the jetting head. This movement continuously places the beneficial agent on the struts of the first portion until the desired surface of the stent has been positioned to receive beneficial agent over the known surface area, and a predetermined quantity of beneficial agent has been dispensed. The beneficial agent is provided on the stent struts and the jetting head thereby does not disperse beneficial agent in areas wherein metal has been removed from the stent. This process may be repeated for subsequent portions of the interventional device, such that known quantities of beneficial agent are provided over each corresponding portion of the interventional device. As with the raster format, flow rate or rate of relative movement can be controlled to adjust local areal density of beneficial agent as desired.

In yet another embodiment, the two-axis positioning system is coupled to a charge-and-deflect jetting head. A charge-and-deflect jetting head is capable of producing a rastered pattern of droplets over a predetermined width of the stent. That is, it is also in accordance with the invention to apply a surface charge to selected droplets of beneficial agent dispensed from the dispensing element. Preferably, if a positive surface charge is applied to the beneficial agent, an antioxidant can be included in the beneficial agent. In this manner, the antioxidant can help to prevent the oxidation of a beneficial agent that might otherwise oxidize when positively charged. Additionally, or alternatively, other known techniques can be used to prevent or inhibit oxidation of beneficial agent. The trajectory of charged droplets of beneficial agent can be altered by a deflection field. For example, an electrode 144 may be used to deflect the trajectory of beneficial agent, which is charged by a charger 142, towards a predetermined portion of the prosthesis as shown in Fig. 7. If desired, a charge opposite that induced on the droplets of beneficial agent can be applied to a predetermined portion of

the prosthesis to provide an electrostatic attraction between the droplets of beneficial agent and the prosthesis for greater accuracy and efficiency.

To effect predetermined loading of beneficial agent, or coating thickness, several methods of controlling the two-axis positioning system in coordination with control of the fluid dispensing are possible so as to result in a precise deposition of beneficial agent on the outer surface of the stent or prosthesis 10. First, the motor 122 that controls rotation of the prosthesis about its longitudinal axis can be turned on to produce a constant angular velocity. A second motor 124 is then controlled to advance the prosthesis or stent in front of the dispensing element 150 at a predetermined rate to generally describe a spiral or helix across the longitudinal axis of the stent, where the pitch width, from rotation to rotation, is the same as the raster width of the dispensing element 150. When a charge-and-deflect dispensing element is used, the surface of the prosthesis 10 or stent can be exposed to the dispensing element 150 in a more rapid manner than for the single drop wide raster pattern that is possible with the drop-on-demand mode system. When the first stent strut is detected to be present in front of the jet head 150, a bit-mapped pattern that has been previously stored in memory 170 to describe the shape of the struts is rastered out by providing appropriate charges on selected droplets. Second, a linear array detector 160 with resolution similar to the number of droplets in each raster line can detect, by reflected or transmitted light, the presence of a stent strut that is about to revolve in front of the jetted fluid window. The data from this type of detector can then be transferred to a shift register which produces the necessary raster data by shifting the bit pattern out a bit at a time. With this method, no predetermined bit-map is necessary, and any slight variations in speed, edge detection or position may be automatically compensated. This process may be repeated for subsequent portions of the interventional device, such that known quantities of beneficial agent are provided over each corresponding portion of the interventional device.

Further in accordance with the invention, a system for loading beneficial agent onto a prosthesis for delivery within a lumen is provided. As shown in Fig. 7 and Fig.13, the system includes a holder 110 for supporting a prosthesis and a fluid-dispenser having a dispensing element 150 capable of dispensing beneficial agent 15 in discrete droplets 155, each droplet having a controlled trajectory.

The holder includes a mandrel or spindle 112 made of any suitable material known in the art. Preferably, however, the spindle 112 comprises a superelastic material, such as

nitinol, or any other material that has shape memory properties. Particularly, manipulation of a stent holder made of stainless steel can result in bending and deformation of the spindle. Such deformation causes poor rotational accuracy and high run-out, *e.g.*, 0.25 -2.5 mm, from one end of the spindle to the other end of the spindle. This can cause a lower efficiency of loading beneficial agent onto a prosthesis, and lower efficiency of droplet interaction with the prosthesis because the position of the stent under the jetting head varies as the run out varies. Superelastic materials generally have properties that are able to absorb and recover from up to 8% strain force. Thus, advantageously, nitinol provides a more resilient spindle capable of undergoing repeated manual stent mounting without the plastic deformation that occurs with a stainless steel spindle design.

For purpose of illustration and not limitation, and as shown in Figure 13, a nitinol spindle 112 may be made using a centerless grinding technique to obtain high concentric accuracy. Despite this grinding process, the centerline of the small diameter part of the spindle (*e.g.*, 0.5 mm diameter) can vary a few degrees from the centerline of the intermediate diameter section (*e.g.*, 2 mm diameter). This variance can be removed by heating the spindle near the junction of the small and intermediate diameter section and bending it to remove most of the residual run out. Upon cooling, the spindle, shown in Fig. 13, assembly retains its new position. The final run out on an exemplary spindle after using these techniques was about 0.051mm.

The system also includes a driver such as a driver assembly 120 to create relative movement between the holder 110 and the dispensing element 150, and a controller 170 in communication with the driver 120 to define a dispensing path of relative movement between the dispensing element 150 and the holder 110. The controller also communicates with the dispensing element 150 for selectively dispensing beneficial agent in a selected format along the dispensing path onto a selected portion of the prosthesis 10 supported by the holder 110. In one aspect of the invention the holder 110 supporting the prosthesis 10 is moveable while the dispensing element 150 remains stationary during dispensing of beneficial agent 15. However, in another aspect of the invention the holder 110 supporting the prosthesis 10 remains stationary while the dispensing element 150 moves along the dispensing path. Alternatively, both the holder 110 and dispensing element 150 are moveable. In another aspect of the embodiment, as previously described, the system includes a detector 160 to detect when the dispensing element 150 is aligned with the predetermined portion of the

prosthesis 10. Various known components can be used in combination for construction of the system of the present invention. For example, jetLab System II from MicroFab Technologies of Plano, Texas, as modified to include the desired features of the invention can be used.

In yet another embodiment of the invention, a determination of the quantity of
5 beneficial agent dispensed over a given or known surface area can be established. According to one aspect, a predetermined ratio of an identifiable marker is added to the beneficial agent and both the beneficial agent and the marker are loaded onto the prosthesis. Subsequently, the amount of identifiable marker loaded onto the prosthesis is detected to determine the amount of corresponding beneficial agent loaded onto the prosthesis. In one aspect of the
10 invention, the identifiable marker includes radiopaque material. After loading the radiopaque material with the beneficial agent onto the prosthesis, the prosthesis is imaged and an intensity value is measured to determine the amount of beneficial agent loaded thereon and thus local areal density. The identifiable marker in this aspect can also include a fluorescent dye, *e.g.*, coumarin dye. In another aspect of the invention, the identifiable marker includes
15 charged particles, for example and not limitation, protons or electrons. After loading the marker and beneficial agent onto the prosthesis the detecting step includes measuring a charge build-up on or current flow from the prosthesis resulting from the charged particles. The charge build-up or current flow therefore generally corresponds to the amount of beneficial agent loaded onto the prosthesis. Alternatively, because the fluid jetting
20 technology of the present invention is inherently digital, the quantity of beneficial agent dispensed can be determined by counting the droplets that have been jetted or dispersed.

In yet another alternative, the amount of beneficial agent loaded can be measured more generally by weighing the stent before the jetting operation and then after the jetting operation. The weight difference corresponds to the drug loaded with the concentration being
25 a function of the jet flow rate along the length of the stent. Yet another method is to integrate the charge build-up on the prosthesis when a charge-and-deflect system is used. Since each droplet in a charge-and-deflect jetting system has had a surface charge injected onto it to enable the droplet to be deflected in an electrostatic field, either the loss of charge at the charging electrode or the accumulation of charge on the prosthesis can be integrated over
30 time to determine the total volume of fluid that has accumulated on the surface of the device.

Also in accordance with the invention, an on-board spectrometer may be utilized for monitoring the beneficial agent concentration on the jetter reservoirs as a function of time. It

is desirable to load beneficial agent such as a drug at a constant concentration. However, due to the evaporation of solvent during the loading process, the concentration of drug will increase. Advantageously, a spectrometer can be configured with a pump to add solvent to the drug such that a constant absorbance on the spectrometer is maintained. The constant
5 absorbance level of the spectrometer is pre-set to monitor an appropriate wavelength. The maintenance of a constant absorbance reading on the spectrometer by the addition of solvent translates to the maintenance of a pre-set drug concentration.

For drop-on-demand jetting systems, this same drug quantification concept can be utilized by adding a constant voltage charging electrode adjacent to the nozzle of the
10 dispenser so as to add a polar charge to each droplet. The coating on the stent, if an insulator, will act as a capacitor to the charge. This detection technique will be able to detect charge build up if a small leakage path is provided or if a second reference surface is provided against which to compare charge build up. Other alternative techniques can be used. For example, if a metal mandrel is present inside the stent it may be used to monitor any lost
15 droplet or splash. The charge that directly transfers to this "electrode" will create an opposite polarity current to the charge presented to the insulated coated surface of the stent.

For each of these detection techniques described above, an appropriate detector can be incorporated in the system of Figure 7, preferably in communication with controller 170.

In accordance with another aspect of the invention, a second beneficial agent or
20 multiple beneficial agents can be loaded onto the prosthesis as described above. Therefore, further in accordance with the invention, an interventional device comprising a prosthesis loaded with a plurality of discrete droplets of a first beneficial agent and a plurality of discrete droplets of a second beneficial agent is provided, such as by using the system and method shown in Fig. 9.

Particularly, the method described in detail above for one beneficial agent can be
25 modified to allow for loading multiple beneficial agents onto a prosthesis, which might ordinarily lead to undesirable results when using conventional loading techniques. For example and not limitation, the first beneficial agent and the second beneficial agent may have different physical and/or chemical characteristics preventing the beneficial agents from
30 being capable of dissolving in the same solvent, or at the same pH or temperature. In particular, the first beneficial agent can be dissolved in a solvent that is immiscible with the solvent in which the second beneficial agent is dissolved. Alternatively, the first beneficial

agent and the second beneficial agent may be incompatible with each other. In particular, the first beneficial agent and the second beneficial agent can be undesirably chemically reactive or may have undesirably different release rates (or contrarily, undesirably similar release rates). Additionally, the first and second beneficial agents can simply be detrimental to each other, e.g., one of the beneficial agents may degrade the efficacy of the other beneficial agent. Thus, although loading the particular multiple beneficial agents onto the same surface of a prosthesis can be desired it often may be problematic due to some incompatibility when using a conventional loading technique. In accordance with the present invention, a method of loading such beneficial agents and an interventional device for the delivery of such beneficial agents is provided.

As noted above, the beneficial agents are loaded in a plurality of discrete droplets on the surface of the prosthesis. The discrete droplets of multiple beneficial agents are preferably loaded onto the prosthesis as unmixed droplets to provide an interspersed pattern or alternatively, the unmixed droplets of beneficial agent can be loaded onto the prosthesis to provide an overlapping pattern of the first beneficial agent and the second beneficial agent. In this manner, the edges of the droplets overlap or alternatively, a larger surface of the droplet overlaps other droplets to provide a layering effect, as depicted in Fig. 10.

Multiple fluid-dispensers preferably are in accordance with the invention, wherein each beneficial agent to be loaded onto the prosthesis is dispensed from a distinct dispensing device. For purpose of illustration and not limitation as shown in Figure 9, a first dispenser 150 is provided with a first beneficial agent 15' dissolved in a solvent that is compatible for that particular first beneficial agent. Further, a second fluid-dispenser 150" is provided with a second beneficial agent 15" that is different from the first beneficial agent 15', and requiring a different solvent for compatibility. For example, the first beneficial agent could be a water-soluble agent, whereas the second beneficial agent could be a water-insoluble agent, each requiring a different solvent. Accordingly, both beneficial agents are loaded onto the same surface of the prosthesis without problems arising from their immiscibility.

Where two fluid-dispensers are used to load the multiple beneficial agents onto the prosthesis, the trajectories of discrete droplets corresponding to each of the first beneficial agent and the second beneficial agent can be aligned such that the droplets from each beneficial agent combine and mix prior to their being loaded on the prosthesis. In this manner, the first and second beneficial agent can form a third beneficial agent which is

loaded onto the prosthesis. For purpose of illustration and not limitation, the first beneficial agent may be bisphenol-A-diglycidyl ether and the second beneficial agent can be triethylenetetramine. Upon combination of the first beneficial agent and the second beneficial agent, a cross linked coating is formed to provide a third beneficial agent. In yet another illustrative example, the first beneficial agent can be bisphenol-A-diglycidyl ether and paclitaxel and the second beneficial agent can be triethylenetetramine. Upon the combination of the two controlled trajectories of beneficial agents, a third beneficial agent is formed, a cross-linked coating entrapping paclitaxel, which is loaded on the prosthesis. Alternatively, the discrete droplets of the first and second beneficial agent can be aligned along trajectories to mix on the surface of the prosthesis.

As noted above, the beneficial agent can include a drug and polymer mixture. In accordance with the method of the invention, the first and second beneficial agents can correspond to drug-polymer mixtures having different concentrations of polymer to effect different release rates of the particular drug in each beneficial agent. For example, the drug-polymer mixture having a higher concentration of polymer would have a slower release of the drug within the lumen than a drug-polymer mixture having a lower concentration. Alternatively, rather than providing drug-polymer mixtures having different polymer concentrations to provide different release rates, it is also possible to dispense beneficial agents using different polymers or other binders, wherein the specific polymer or binder has different diffusivity or affinity to assure delivery of the beneficial agents at different rates. Thus, in accordance with the invention, multiple beneficial agents can be released at rates appropriate for their activities, such that the prosthesis of the invention has multiple beneficial agents which elute off the prosthesis at desired rates.

For example, a cationic phosphorylcholine-linked polymer which has a higher affinity for anionic therapeutic agents can be blended and dispersed as a first beneficial agent and lipophilic phosphorylcholine-linked polymer can be blended with lipophilic drugs as the second beneficial agent to effect different release rates respectively.

In yet another embodiment of the invention, one of the first and second beneficial agents loaded onto the prosthesis can be more hydrophobic or less water-soluble than the other. Thus, in accordance with the invention is provided a prosthesis including first and second beneficial agents wherein one of the beneficial agents is more hydrophobic or less water soluble than the other. In this manner, the more hydrophobic beneficial agent acts as a

water barrier or hydration inhibitor for the less hydrophobic beneficial agent, thereby reducing the release rate of the less hydrophobic beneficial agent as disclosed in US Provisional Patent Application 60/453,555 and PCT/US03/07383, each of which was filed on March 10, 2003, and each of which is incorporated herein by reference thereto.

5 In addition to providing a prosthesis having multiple beneficial agents which are delivered at unique or desired rates, according to another aspect of the invention, the first beneficial agent can be dissolved in solvent wherein the second beneficial agent causes the first beneficial agent to precipitate out of the solvent. For example and not limitation, the first beneficial agent may be rapamycin dissolved in ethanol, and the second beneficial agent may
10 be water. Upon droplet combination using the method and system of the invention, the rapamycin will precipitate within the droplet and be deposited on the prosthesis as a microprecipitate.

In yet another aspect of the invention, at least one of the first and second beneficial agents can be mixed with a binder prior to being loaded onto the prosthesis. Further in
15 accordance with this aspect one of the beneficial agents can be a curative agent for curing the binder on the prosthesis with the beneficial agent mixed therein. For example, see Example 4 below.

As noted above, one of the beneficial agents can be a solvent for the other beneficial agent. Thus, in accordance with the invention, the first beneficial agent, *e.g.*, a drug,
20 polymer, or a combination thereof, can be loaded onto the prosthesis, and subsequently the second beneficial agent, *i.e.*, a solvent, can be loaded onto the prosthesis so as to redistribute the first beneficial agent more uniformly along the prosthesis.

As also noted above, the prosthesis can include at least one reservoir or cavity or trough therein. For purpose of illustration and not limitation, computer controlled profiles of
25 a laser cut stent can be utilized to precisely deposit beneficial agent into the laser cuts on the stent struts. For example, a longitudinal trough can be laser cut, etched, or otherwise formed into the strut, such as in the curve or bend of the strut for instance. In accordance with a preferred aspect of the invention, the cavity or trough is provided with a contoured cross-sectional profile for retention and elution of beneficial agent therein. Particularly, and as
30 depicted schematically in Figure 12, the cross-sectional profile of the cavity or trough 16 includes a smaller dimension at the interface with the strut surface, so as to define a mouth 17 of the trough 16, and a larger internal cross-dimension of the trough to define a reservoir 18.

Figure 12 shows one such embodiment, wherein mouth 17 is defined for reservoir 18 of trough 16. Use of the fluid jet system and method of the present invention thus allows for beneficial agent to be loaded into the mouth 17 of trough 16, without the entrapment of air within the reservoir 18. An appropriate volume of beneficial agent is deposited in the laser cut profile to at least partially fill the reservoir 18. In this respect, beneficial agent that is deposited in the longitudinal trough can include a combination of drugs or a combination of polymers or a combination of drugs and polymers in different layers. Furthermore, different layers of polymer and/or drug having different concentrations, or different drug elution rates can be loaded therein. Additionally, an interim polymer and/or final polymer overcoat can be applied over the beneficial agent. Such a deposition configuration in combination with cavities is particularly beneficial for minimizing delamination of the polymer-drug layers, and also provides versatility in controlling drug elution and the generation of various combinations of drug release patterns. A computer profiling approach is also useful to coat drug and polymer layers on the distal and proximal edges of the stent.

In accordance with another aspect of the invention, one or more of the reservoirs or cavities or troughs is loaded with a more hydrophilic first beneficial agent and then a second more hydrophobic beneficial agent is loaded onto the first beneficial agent within the cavity or reservoir in a manner as described above.

Further in accordance with the invention, using the method and systems described above, a first beneficial agent loaded onto the prosthesis can have a first local areal density and a second beneficial agent loaded onto the prosthesis can have a second local areal density. As used herein, "areal density" refers to the amount of beneficial agent per unit surface area of a selected portion of the prosthesis. "Local areal density" refers to the dosage of beneficial agent per local surface area of the prosthesis. The local areal density of the first beneficial agent and the local areal density of the second beneficial agent can be uniform across each respective portion to define stepped changes in local area density as depicted in Figure 1b or can be varied across a selected portion of the prosthesis to define gradients of local area density, as depicted in Figure 1c. Accordingly, an interventional device is provided having a prosthesis that is at least partially loaded with beneficial agent having a local areal density that is varied along a selected portion of the body of the prosthesis.

In accordance with a preferred embodiment, the prosthesis has a tubular body when deployed in a lumen. Preferably, the tubular body includes a first and second portion at least

partially loaded with beneficial agent such that the first portion has a first local areal density and the second portion has a second local areal density. Each portion may be defined as a preselected length of the prosthesis. Alternatively, as shown in Fig. 1b, the first portion can be defined by a selected set of interconnected structural members and the second portion can be defined as a second set of interconnected members *e.g.*, connectors elements or ring-elements. For example and not limitation, at least one of the first and second set of selected interconnected elements can define at least one ring-shaped element extending around the circumference of the prosthesis.

In another embodiment of the invention, the local areal density is varied as a continuous gradient along a selected portion of the prosthesis as shown in Fig. 1c. Accordingly, in one aspect of the invention the local areal density of beneficial agent is varied such as to provide a prosthesis having a local areal density of beneficial agent at the ends of the prosthesis that is different than the local areal density of beneficial agent at an intermediate section of the prosthesis. For purpose of illustration and not limitation, the local areal density of beneficial agent at the intermediate section of the prosthesis can be greater than that at the proximal and distal ends of the prosthesis as shown in Figure 1c.

Alternatively, the proximal and distal ends of the prosthesis can have a greater local areal density of beneficial agent than that on the intermediate section of the prosthesis. In a preferred embodiment of the invention, the varied local areal density of beneficial agent corresponds to the location of a lesion when the prosthesis is deployed within a lumen. For example, the prosthesis can be loaded to have a greater local areal density of beneficial agent along a preselected portion of the prosthesis that corresponds to the location of the lesion when the prosthesis is deployed in a lumen. Thus, targeted therapy may be achieved with the interventional device of the present invention.

In accordance with the invention, the local areal density can be varied by varying the relative rate in which beneficial agent is loaded to a selected location along the prosthesis. To this end, the frequency in which the droplets of beneficial agent are applied along a unit length of the dispensing path to the prosthesis is varied. Alternatively, the relative rate of loading beneficial agent can be varied by varying the relative movement between the dispensing element and the prosthesis. Another alternative for varying the relative rate of loading beneficial agent is to vary the amount of beneficial agent per droplet dispensed from the dispensing element. Other alternatives for varying the local areal density of beneficial

agent loaded onto the prosthesis include mixing the beneficial agent with a binder and varying the ratio of beneficial agent to binder. Alternatively, the amount of the mixture of beneficial agent and binder that is applied to the prosthesis can be varied to achieve a varied local areal density of beneficial agent. Other methods of varying the local areal density of beneficial agent known in the art may be used.

As noted above, the beneficial agent is at least partially loaded onto a surface of the prosthesis. Further in accordance with the invention the prosthesis includes a first surface and a second surface that are at least partially loaded with beneficial agent. In one embodiment of the invention, the first surface and the second surface each correspond to one of the inner surface and the outer surface of the prosthesis. Thus, according to this particular embodiment, beneficial agent, as defined above, is loaded onto the inner or luminal surface of a prosthesis as well as the outer surface of the prosthesis. The method described above can be used for this aspect of the invention, wherein the beneficial agent is loaded on the inner surface of the prosthesis by inserting a fluid dispensing element within the inner diameter of the prosthesis, or by dispensing beneficial agent diametrically across the prosthesis between structural members 12 to impact the inner surface on the opposite side of the prosthesis 10 as shown in Fig. 11. In this regard, the dispensing element 150" is aligned so that the controlled trajectory 152" of discrete droplets 155" of beneficial agent optimally intersect with the inner surfaces of the structural features of the prosthesis 10 and not intersect with the structural features of the outer surface of the prosthesis. For purposes of illustration and not limitation, for a prosthesis comprising an odd number of radial repeats in the pattern of structural features, the preferred alignment of the dispensing element is orthogonal to the central axis of the prosthesis and in a plane that intersects the central axis of the prosthesis. However, for a prosthesis comprising an even number of radial repeats in the pattern of structural features, the preferred alignment of the dispensing element to the prosthesis is orthogonal to the central axis of the prosthesis, but in a plane that does not intersect the central axis of the prosthesis. As another example, for a prosthesis including a tubular member comprising multiple radially and axially repeating structural elements, the preferred alignment of the dispensing element can be determined by assessing the shadow cast by the foreground or outer structural elements on the background or inner structural elements. The preferred plane to align the dispensing element can be determined by

assessing the plane in which the maximum amount of unobstructed inner surface is presented upon rotation of the tubular member.

In accordance with this aspect of the invention, the relative motion of the dispensing element and the prosthesis can be coordinated to enable a preprogrammed "raster" image of the position or locations of the structural elements of the inner surface. Alternatively, the vector pattern of the structural elements may be preprogrammed, as previously described. Also, in accordance with the invention, the beneficial agent is dispensed from the dispensing element along a controlled trajectory that is substantially tangential to or near the outer surface of the prosthesis and is loaded on the inner surface of the structural elements of the prosthesis.

In this aspect of the invention, the interventional device can be designed to provide combination therapy of beneficial agents to targeted locations. For example and not limitation, the particular beneficial agent loaded to the luminal or inner surface of the prosthesis can be intended for systemic release, whereas the particular beneficial agent loaded onto the outer surface of the prosthesis is intended for release into the wall of the lumen. In accordance with one aspect of the invention, the beneficial agents loaded onto the luminal side or inner surface of the prosthesis include, without limitation, antiplatelet agents, aspirin, cell adhesion promoters, agents that promote endothelial recovery, agents that promote migration, and estradiol. The beneficial agents loaded onto the outer surface of the prosthesis include without limitation, anti-inflammatories, anti-proliferatives, smooth muscle inhibitors, cell adhesion promoters, and the rapamycin analog ABT-578, i.e., 3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-3-methoxy-4-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentacontine-1,5,11,28,29(4H,6H,31H)-pentone; 23,27-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentacontine-1,5,11,28,29(4H,6H,31H)-pentone.

In accordance with another embodiment of the invention, the first surface of the prosthesis is defined by a plurality of interconnecting structural members. Accordingly, the first surface can include a first selected set of structural members, *e.g.*, a connector member, and the second surface can include a second selected set of the structural members, *e.g.*, a ring-shaped element extending around the circumference of the prosthesis.

As noted above, the beneficial agent is loaded onto the prosthesis to provide a controlled local areal density across a length of the interventional device. That is, it may be desirable to provide a greater concentration of beneficial agent at one portion of a prosthesis and a lower concentration, or perhaps no beneficial agent, at another portion of the prosthesis.

5 For example, in one preferred embodiment, a greater local areal density can be provided at a first portion, *e.g.*, intermediate portion 10b, of a stent 10, as shown in Fig. 1a, while providing a lower local areal density of beneficial agent to a second portion, *e.g.*, one or both end portions (10a, 10c), of the stent 10. In accordance with the present invention, each of the first and second portions of the prosthesis may be defined by any of a variety of patterns or
10 selected portions of the prosthesis. For example, the first portion of the prosthesis can be defined by longitudinal connectors whereas the second portion of the stent is defined by annular rings, or vice versa, as illustrated in Figure 6.

In accordance with another aspect of the present invention, the interventional device includes a first prosthesis and a second prosthesis in combination to define an overlapping
15 portion and at least one non-overlapping portion. For example, and as embodied herein, Figures 2 or 3 present a schematic representation of a nested interventional device including a first prosthesis 20 and a second prosthesis 30 configured to be deployed in an overlapping relationship. The interventional device, however, can optionally include more than two
20 prostheses in combination, if desired. Such interventional devices 50 include but are not limited to nested stents and modular bifurcated stents. For purpose of illustration and not limitation, Figure 2 shows a first prosthesis 20 having a first portion 20a and a second portion 20b and a second prosthesis 30 having a first portion 30a and a second portion 30b. As shown schematically, the beneficial agent distribution profile includes a first local areal density of beneficial agent on one of the first and second portions of one or both of the first
25 prosthesis and the second prosthesis. For example and not by limitation, the first portion 20a of the first prosthesis 20 has half the local areal density of beneficial agent as compared to the second portion 20b of the first prosthesis 20. The first portion 30a of the second prosthesis 30, likewise, has half the local areal density of beneficial agent compared to the second portion 30b of the second prosthesis 30. In this manner, when the ends of two stents are
30 superimposed or deployed in an overlapping relationship 25 during a procedure, the local areal density of beneficial agent along the interventional device 50 is controlled so as to be

uniform. If desired, alternative concentrations can be provided on each portion so as to provide the desired effect in combination.

In accordance with the present invention, as shown in Figure. 3, a controlled local areal density of beneficial agent is thus provided across a length of the interventional device
5 50 upon combination of the first prosthesis having first portion 20a and second portion 20b with the second prosthesis having first portion 30a and second portion 30b, as shown in Figure 2. In particular, as shown in Figure 3, the overlapping segment 25 of first prosthesis 20 and the second prosthesis 30 has an equal local areal density of beneficial agent as compared to non-overlapping segments 20b and 30b.

10 Alternatively, the beneficial agent distribution profile for the interventional device may be controlled to include any of a variety of desired patterns. For example, the interventional device can have a decreased local areal density of beneficial agent on the distal and proximal ends of each prosthesis body, as noted above. This profile is highly desirable in preventing adverse dosing of beneficial agent if multiple prostheses are placed in
15 combination with each other but still provides for decreased dosage of the extreme ends of the interventional device as a whole. Alternatively, as embodied herein, the beneficial agent distribution profile can provide a controlled local areal density that is uniform along the length of first prosthesis and second prosthesis in combination, or multiple prostheses in combination. Alternatively, in accordance with the invention, the beneficial agent
20 distribution profile provides a controlled local areal density that is varied along the length of the first prosthesis and the second prosthesis in combination, or multiple prostheses in combination.

For illustration purposes, overlapping or nested prostheses, as shown in Figure 3, can have beneficial agent distribution profiles such that the controlled local areal density of
25 beneficial agent of a non-overlapping segment is in fact greater than the controlled local areal density of beneficial agent of an overlapping segment. Similarly, the alternative can also be true; that an overlapping segment is controlled to have a greater or different local areal density of beneficial agent than a non-overlapping segment. Advantageously, this feature also enables selective dosing of beneficial agent to a targeted area when using multiple prostheses
30 in combination, as well as a single prosthesis alone. Selective dosing of beneficial agent to a targeted area means that the beneficial agent can be applied to the prosthesis or prostheses in combination such that the desired beneficial agent is loaded onto the prosthesis in a selective

pattern so that the beneficial agent or beneficial agents are released from the prosthesis in close proximity to a targeted location. Fluid jetting as previously described is particularly preferred for selective dosing.

5 In accordance with the present invention, and as embodied schematically in Figure 5, a bifurcated interventional device also can be provided, which includes a first prosthesis 20' and a second prosthesis 30' in combination to define an overlapping portion 50' and non overlapping portions 20b', 30b'. For purposes of illustration and not limitation, Figure 4 shows a first prosthesis 20' having a first portion 20a' and a second portion 20b', and a second prosthesis 30' having a first portion 30a' and a second portion 30b'. As shown for purpose of
10 illustration and not limitation, the beneficial agent distribution profile includes a first local areal density of beneficial agent on one of the first and second portions of one or both of the first prosthesis 20' and the second prosthesis 30'. For example, and not by limitation, the first portion 20a' of the first prosthesis 20' has half the local areal density of beneficial agent as compared to the second portion 20b' of the first prosthesis. The first portion 30a' of the
15 second prosthesis 30' has half the local areal density of the second portion 30b' of the second prosthesis 30'. In accordance with the present invention, as shown in Figure 5, a controlled local areal density of beneficial agent is thus provided across a length of the bifurcated interventional device 50 upon combination of the first prosthesis having first portion 20a' and second portion 20b' with the second prosthesis having first portion 30a' and second portion
20 30b', as shown in Figure 4.

Another feature of the present invention includes applying a layer of base material on a selected portion of the prosthesis described above. The beneficial agent is loaded onto the base material layer according to the methods described above. The base material layer preferably defines a pattern for loading the beneficial agent onto the prosthesis.

25 The present invention also encompasses, for any of the embodiments disclosed, the application of a rate-controlling topcoat over the beneficial agent loaded prosthesis for further controlling or sustaining the release of beneficial agent. The rate-controlling topcoat may be added by applying a coating layer posited over the beneficial agent loaded prosthesis. The thickness of the layer is selected to provide such control. Preferably, the overcoat is applied
30 by fluid-jet technology. Advantageously, fluid jetting an overcoat such as a polymer overcoat allows a thinner and more uniform layers. However other conventional methods can

be used such as other fluid-dispensers, vapor deposition, plasma deposition, spraying, or dipping, or any other coating technique known in the art.

The present invention also provides a method for manufacturing an interventional device for delivery of beneficial agent. This method comprises the steps of providing a first
5 prosthesis to be deployed within a lumen; providing a second prosthesis configured to be deployed in an overlapping relationship with the first prosthesis, the first prosthesis and the second prosthesis in combination defining at least one non-overlapping segment and an overlapping segment; and loading the first prosthesis and the second prosthesis with
10 beneficial agent to provide a controlled local areal density along a length of the first prosthesis and the second prosthesis in combination. The method described in detail above is preferred for such loading step.

The present invention also provides a method of delivering beneficial agent. In accordance with this method, as described in detail in conjunction with the description of the interventional device of the present invention above, the method comprising the steps of
15 providing a first prosthesis having a tubular body when deployed in a lumen; providing a second prosthesis having a tubular body when deployed in a lumen; loading at least one of the first prosthesis and the second prosthesis with beneficial agent; deploying the first prosthesis into a lumen; deploying the second prosthesis into the lumen to define in combination with the first prosthesis at least one non-overlapping segment and an
20 overlapping segment; wherein the beneficial agent is loaded onto at least one of the first prosthesis and the second prosthesis to provide a controlled local areal density of beneficial agent across a length of the first prosthesis and the second prosthesis when deployed. The method described in detail above is preferred for such loading step.

The present invention will be further understood by the examples set forth below, which are
25 provided for purpose of illustration and not limitation.

EXAMPLES

Example 1: Jetting of reactive substances

30 The components of a commercial two-part epoxy formulation are mixed by the jetting process and applied to a surface to form a coating. In a formulation manufactured by Buehler, Lake Bluff IL, one part is a liquid "epoxide resin" that contains 4,4'

isopropylidenediphenol epichlorohydrin resin and butyl glycidyl ether. The second part is a liquid “hardener” that contains diethylene triamine, triethylene tetramine, and polyoxypropylenediamine. In the jetting process, one reagent jet system (A) is loaded with epoxide resin and a second jetting system (B) is loaded with hardener. The jets are aligned such that the droplets emanating from each jet combine in midair and travel to the target device to form a crosslinked coating, after a curing time of 2 – 8 hours. The volume of a droplet emanating from jet A is 5 times larger than the volume of a droplet emanating from Jet B and the total number of droplets dispensed from each jet are approximately equal.

10 Example 2: Jetting of reactive substances

The components of a commercial two-part epoxy formulation are mixed by the jetting process and applied to a surface to form a coating. In a two part commercial formulation manufactured by Buehler, Lake Bluff IL, one part is a liquid “epoxide resin” which contains 4,4' isopropylidenediphenol epichlorohydrin resin and butyl glycidyl ether. The second part is a liquid “hardener” that contains diethylene triamine, triethylene tetramine, and polyoxypropylenediamine. In the jetting process, one reagent jet system (A) is loaded with epoxide resin and a second jetting system (B) is loaded with hardener. The jets are aligned such that the droplets emanating from each jet combine in midair and travel to the target device to form a crosslinked coating, after a curing time of 2 – 8 hours. The volume of a droplet emanating from jet A is 4 times larger than the volume of a droplet emanating from Jet B and the total number of droplets dispensed from each jet are approximately equal. This coating cures at a faster rate than the coating described in example 1.

Example 3: Jetting of reactive substances

25 The components of a commercial two-part epoxy formulation are mixed by the jetting process and applied to a surface to form a coating. In a two part commercial formulation manufactured by Buehler, Lake Bluff IL, one part is a liquid “epoxide resin” which contains 4,4' isopropylidenediphenol epichlorohydrin resin and butyl glycidyl ether. The second part is a liquid “hardener” that contains diethylene triamine, triethylene tetramine, and polyoxypropylenediamine. In the jetting process, one reagent jet system (A) is loaded with epoxide resin and a second jetting system (B) is loaded with hardener. The jets are aligned such that the droplets emanating from each jet combine in midair and travel to the target

device to form a crosslinked coating, after a curing time of 2 – 8 hours. The volume of a droplet emanating from jet A is approximately equal to the volume of a droplet emanating from Jet B, but the total number of droplets dispensed from jet A is 4 times more than from jet B.

5

Example 4: Formation of a crosslinked network containing biologically active agents

One reagent jet system (A) is loaded with a liquid epoxide resin and a solubilized formulation of the drug, paclitaxel, 20 % by weight with respect to the epoxide resin. A second jetting system (B) is loaded with hardener similar to that described in example 1 combined with an equal weight or less of a biocompatible polymer. One example of such a species is a phosphorylcholine linked polymer of the general formula poly(MPC_w:LMA_x:HPMA_y:TSMA_z), where MPC is 2-methacryoyloxyethylphosphorylcholine, LMA is lauryl methacrylate, HPMA is hydroxypropyl methacrylate and TSMA is trimethoxysilylpropyl methacrylate. This polymer is dissolved in a solvent such as chloroform. The jets are aligned such that the droplets from each jet combine in midair and travel to the target device to form a crosslinked coating entrapping the drug and polymer. The volume of a droplet emanating from jet A is 5 times larger than the volume of a droplet emanating from jet B and the total number of droplets dispensed from each jet are approximately equal. The coating is heated for 4 hours at 70 degrees C to cause crosslinking of the phosphorylcholine-linked polymer predominantly with itself by means of the trimethoxysilane groups, and simultaneously accelerating the curing of the epoxide resin with the hardener.

10

15

20

Example 5: Formation of a drug microprecipitate

One reagent jet system (A) is loaded with rapamycin dissolved in ethanol. A second jetting system is loaded with water. The droplet volume of one drop emanating from jet A is 50 picoliters and the droplet volume of one drop emanating from Jet B is 150 picoliters. The jets are aligned such that the droplets from each jet combine in midair and travel to the target device. During the droplet combination the rapamycin will precipitate within the droplet and be deposited on the target surface as a microprecipitate.

25

30

Example 6: Loading of Drug onto a Polymer Base- Coated Coronary Stent

In a demonstration of feasibility, a stock jetting solution of 20 mg/ml ABT-578 + 4 mg/ml phosphorylcholine-linked methacrylate polymer (PC) in isobutanol was prepared. A fluid jetting system manufactured by MicroFab Technologies of Plano, Texas was programmed to jet 75 micrograms of drug evenly over a 1.4 x 11 mm OC BiodivYsio stent to obtain an areal density of 5 micrograms per linear mm. Jetting of 21,888 drops into a vial containing 10 ml of isobutanol gave 77 micrograms of ABT-578 as determined spectrophotometrically at 278nm. Under these conditions, 1 drop was 170 - 180 picoliters and had a diameter between 67 and 70 microns. The stent contained a base coating of phosphorylcholine-linked methacrylate polymer (PC). It was mounted on a fixture that included a mandrel that provided for controlled rotation (θ) about a central axis coaxial with the stent and a stage that provided for lateral movement (X) along the axis of the stent. The motion control was set up to rotate the stent a total of 720 degrees. A view orthogonal to the axis of the rotating stent showed two possible tangential off-axis positions, approximately 50 microns inside a point tangent to the outer surface of the stent, one on each side of the rotation centerline, that provided relatively few instances where a jet trajectory would not impinge on at least one stent structural element. One of these off-axis positions was first selected to start the drug loading. A mandrel mounted stent was positioned so that the trajectory of jetted droplets would impinge on the stent struts at this "off-axis" location. The motion controller was set up to move the stent axially in the X direction and began its motion at a position where the jet trajectory was off the end of the stent. The motion controller ramped up to a predetermined velocity and turned on the fluid jetting head as soon as motion along the X axis reached constant velocity and the end of the stent struts were in a position directly under the jet head. Every time the stent passed completely under the jet head along this off-axis path in the X direction, the motion controller would then ramp down the velocity, stop and rotate the stent 5 degrees. The linear direction was reversed and the next pass was made. After 360 degrees was reached, (72 passes) the table was translated approximately a distance equal to the internal diameter of the stent (1 ID) to the other off-axis position and 72 more passes were made for an additional rotation of 360 degrees. Each stent was thus jetted twice to obtain its drug loading.

Seven (7) stents were loaded with drug. Observation of drug-loaded stents under a stereomicroscope indicated that no webbing occurred between stent struts and the surfaces

were cosmetically smooth. The stents were subsequently extracted into isobutanol for measurement of the drug obtained and the results are shown below.

| | <u>Stent</u> | <u>ABT-578 (micrograms)</u> |
|----|--------------|-----------------------------|
| 5 | 1 | 70 |
| | 2 | 72 |
| | 3 | 69 |
| | 4 | 69 |
| 10 | 5 | 53 |
| | 6 | 61 |
| | 7 | 60 |

15 The average loading obtained was 65 micrograms. The calculated capture efficiency was 84% based on the number of counted droplets of drug dispensed.

20

Example 7: Loading of PC-Coated Peripheral Stents by Reagent Jetting

In a similar feasibility demonstration experiment, a fluid jetting system manufactured by
 25 MicroFab Technologies of Plano, Texas was programmed to dispense 59,904 drops, approximately 3X that used for the 11 mm OC stent. These peripheral vascular stents (SFA) were 5 X 30 mm and were mounted on a larger sized rotation fixture. The stent matrix was much more open than seen on the OC coronary stent; however, good capture efficiency was obtained.

30 stent ABT-578 (micrograms)

| | | |
|----|---------|----------|
| | 1 | 187 |
| | 2 | 176 |
| | 3 | 185 |
| 35 | average | 183 Avg. |

The jetter dispensed 211 micrograms of drug per stent, having a capture efficiency of 86%.

40

Example 8: Overcoating of a Drug-Loaded Stent with Polymer

A 10 mg/ml solution of phosphorylcholine-linked methacrylate polymer (PC) was made in isobutanol. A total of 288 passes along the axial dimension of the stent and over 1440 degrees of rotation under the conditions used in previous examples, produced an overcoat at 5 micrograms per linear mm.

Example 9: Overcoating of a Drug-Loaded Stent with Polymer Having a Variable Areal Density.

A 10 mg/ml solution of phosphorylcholine-linked methacrylate polymer (PC) is made in isobutanol. The linear travel speed of the stent under the jet head is programmed to be 50% slower during the beginning 25% of the stent length and the ending 25% of length. The jetting rate is not varied over the length of the stent. A total of 288 passes along the axial dimension of the stent and over 1440 degrees of rotation are made. Under these conditions, the stent obtains an increased amount of PC on both ends of the stent compared to the middle regions.

Example 10: Drug-Loaded Stent Having a Variable Areal Density of Drug

A stock jetting solution of 20 mg/ml ABT-578 + 4 mg/ml phosphorylcholine-linked methacrylate polymer (PC) in isobutanol is prepared. The linear travel speed of the stent under the jet head is programmed to be 50 % faster during the beginning 25% of the stent length and the ending 25% of length. The jetting rate is not varied over the length of the stent. A total of 144 passes along the axial dimension of the stent and over 720 degrees of rotation are made. Under these conditions, the stent obtains a decreased amount of ABT-578 on both ends of the stent compared to the middle regions.

It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. For example, a charge-and-deflect dispenser can be replaced with a drop-on-demand fluid jetter, or vice versa. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and

or methods of use of the invention, can be made without departing from the spirit and scope thereof.

CLAIMS

What is claimed is:

1. An interventional device for the delivery of multiple beneficial agents, the device comprising:
5 a prosthesis to be deployed in a lumen, the prosthesis having a surface;
a plurality of discrete droplets of a first beneficial agent loaded on the surface of the prosthesis; and
a plurality of discrete droplets of a second beneficial agent loaded on the surface of the prosthesis.
10
2. The interventional device of claim 1, wherein the first beneficial agent and the second beneficial agent are incompatible.
3. The interventional device of claim 1, wherein the first beneficial agent is dissolved in a first solvent and the second beneficial agent is dissolved in a second solvent, and further wherein the first solvent and the second solvent are immiscible.
4. The interventional device of claim 1, wherein the discrete droplets of the first beneficial agent are loaded along a first controlled trajectory and the discrete droplets of the second beneficial agent are loaded along a second controlled trajectory; the first controlled trajectory and the second controlled trajectory being aligned to allow the first beneficial agent
5 and the second beneficial agent to mix prior to being loaded onto the surface of the prosthesis.
5. The interventional device of claim 1, wherein the discrete droplets of the first beneficial agent and the discrete droplets of the second beneficial agent mix on the surface of the prosthesis.
6. The interventional device of claim 1, wherein the first beneficial agent is dissolved in a solvent and the second beneficial agent causes the first beneficial agent to precipitate out of the solvent.

7. The interventional device of claim 1, wherein the first beneficial agent and the second beneficial agent are loaded on the prosthesis in unmixed droplets to provide a selected pattern.

8. The interventional device of claim 1, wherein at least one of the first beneficial agent and the second beneficial agent is mixed with a binder prior to being loaded on the prosthesis.

9. The interventional device of claim 8, wherein the binder is a phosphorylcholine-linked polymer.

10. The interventional device of claim 8, wherein the second beneficial agent cures the binder on the prosthesis with the first beneficial agent mixed therein.

11. The interventional device of claim 8, wherein the first beneficial agent is mixed with a binder having a first release rate for delivery of the first beneficial agent.

12. The interventional device of claim 11, wherein the second beneficial agent is mixed with a binder having a second release rate for delivery of the second beneficial agent; the first release rate being different than the second release rate.

13. The interventional device of claim 1, wherein the prosthesis includes at least one cavity defined therein, the at least one cavity being at least partially loaded with a base material; and further wherein the first beneficial agent and the second beneficial agent are loaded to the base material.

5

14. The interventional device of claim 1, wherein the prosthesis includes at least one cavity, the at least one cavity defining a mouth having a first cross-dimension and a reservoir having a second cross-dimension, the second cross-dimension being greater than the first cross-dimension.

5

15. The interventional device of claim 1, further including a plurality of discrete droplets of a third beneficial agent loaded on the surface of the prosthesis.

16. The interventional device of claim 15, wherein the first beneficial agent is dexamethasone, the second beneficial agent is estradiol, and the third beneficial agent is the rapamycin analog 3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-
5 [(1S,3R,4R)-3-methoxy-4-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone; 23,27-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.
17. The interventional device of claim 15, wherein the first beneficial agent, the second beneficial agent and the third beneficial agent are each dissolved in a first solvent.
18. The interventional device of claim 1, wherein at least one of the first beneficial agent and the second beneficial agent is selected from a group consisting of antithrombotics, anticoagulants, antiplatelet agents, anti-lipid agents, thrombolytics, antiproliferatives, anti-inflammatory, agents that inhibit hyperplasia, smooth muscle cell inhibitors, antibiotics,
5 growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters, antimetotics, antifibrins, antioxidants, antineoplastics, agents that promote endothelial cell recovery, antiallergic substances, radiopaque agents, viral vectors, antisense compounds, oligonucleotides, cell permeation enhancers, angiogenesis agents, paclitaxel, rapamycin, Everolimus, heparin, estradiol, dexamethasone, analogs thereof, rapamycin analog is
10 3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-3-methoxy-4-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone; 23,27-Epoxy-3H-pyrido[2,1-c][1,4]
15 oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone, and combinations thereof.
19. The interventional device of claim 1, further including an overcoat applied over at least a portion of the surface.

20. The interventional device of claim 1, wherein beneficial agent is applied to the prosthesis using a fluid jet dispenser having a dispensing element capable of dispensing beneficial agent in discrete droplets, each droplet having a controlled trajectory.

21. An interventional device for delivery of beneficial agent, the device comprising: a prosthesis to be deployed in a lumen, the prosthesis having a first surface and a second surface; the first surface of the prosthesis at least partially loaded with a first beneficial agent; and the second surface at least partially loaded with a second beneficial agent;

5 at least one of the first beneficial agent and the second beneficial agent being loaded by a fluid-dispenser having a dispensing element capable of dispensing beneficial agent in discrete droplets, each droplet having a controlled trajectory.

22. The interventional device of claim 21, wherein the prosthesis has a tubular body when deployed, the tubular body defining a longitudinal axis; and further wherein the first surface of the prosthesis is defined as an inner surface of the tubular body and the second surface of the prosthesis is defined as an outer surface of the tubular body.

5

23. The interventional device of claim 21, wherein at least one of the first beneficial and second beneficial agent is selected from a group consisting of antiplatelet agents, aspirin, cell adhesion promoters, agents that promote endothelial healing, agents that promote migration, angiogenesis promoters, cytokines, anti migrative agents, antifibrins, estradiol, anti-
5 inflammatories, anti-proliferatives, smooth muscle inhibitors, cell adhesion promoters, and 3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-
9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-3-methoxy-4-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-
6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-
10 1,5,11,28,29(4H,6H,31H)-pentone; 23,27-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone, and combinations thereof.

24. The interventional device of claim 21, wherein the prosthesis is

defined by a plurality of interconnecting structural members; the first surface of the prosthesis including a first selected set of the structural members and the second surface of the prosthesis including a second selected set of the structural members.

5

25. The interventional device of claim 24, wherein at least one of the first selected set of structural members and the second selected set of structural members defines at least one ring-shaped element extending around a circumference of the tubular body.

26. The interventional device of claim 21, wherein the first beneficial agent has a first local areal density and the second beneficial agent has a second local areal density.

27. The interventional device of claim 26, wherein at least one of the first local areal density and the second local areal density is uniform across a selected portion of the prosthesis.

28. The interventional device of claim 21, wherein at least one of the first local areal density of beneficial agent and the second local areal density is varied across a selected portion of the prosthesis.

29. The interventional device of claim 21, further including a third beneficial agent loaded on at least one of the first surface and second surface of the prosthesis.

30. The interventional device of claim 21, the prosthesis further includes a base material layer, the base material layer defining a pattern on the prosthesis for loading the beneficial agent.

31. The interventional device of claim 21, further including an overcoat applied to at least one of the inner surface or the outer surface of the prosthesis.

1/11

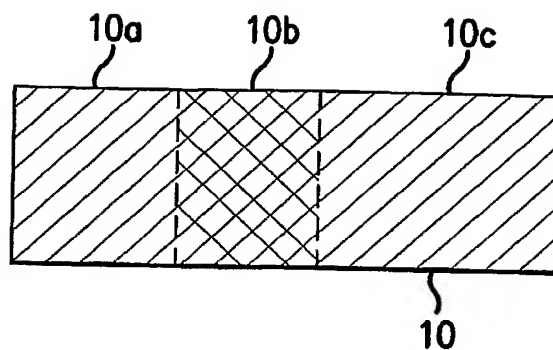


FIG. 1a

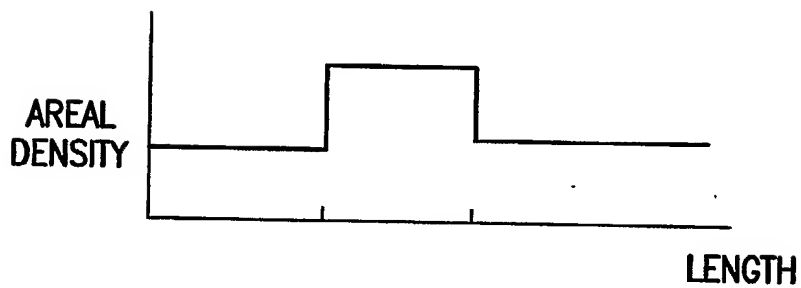


FIG. 1b

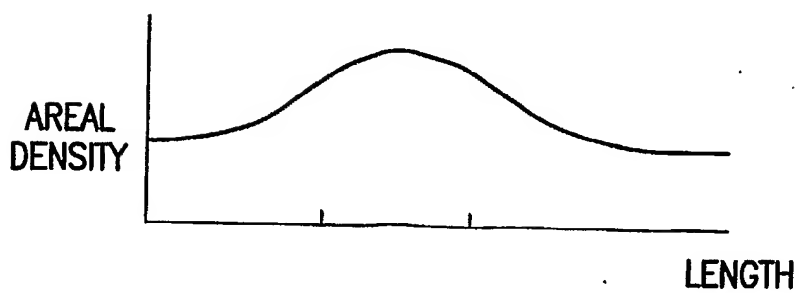


FIG. 1c

2/11

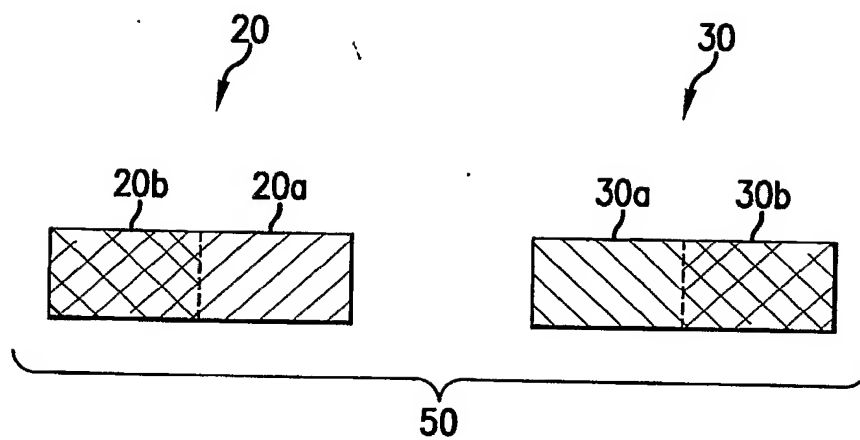


FIG. 2

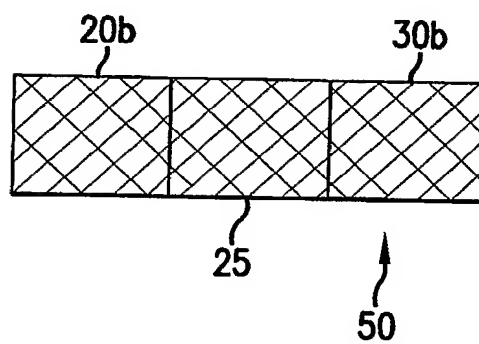


FIG. 3

3/11

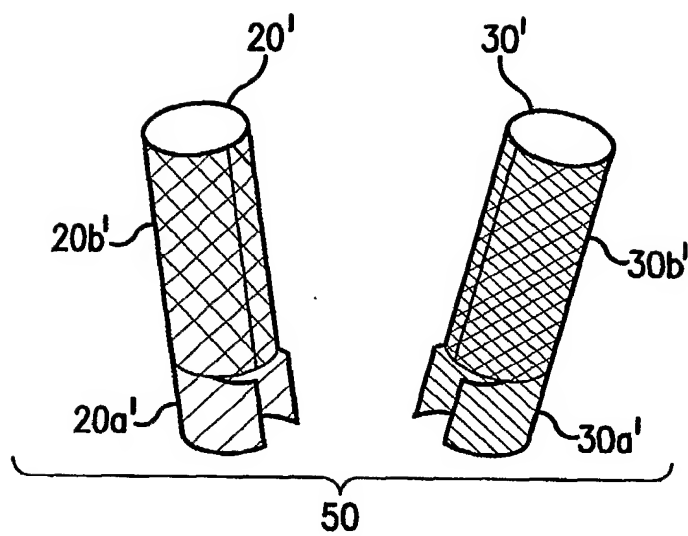


FIG. 4

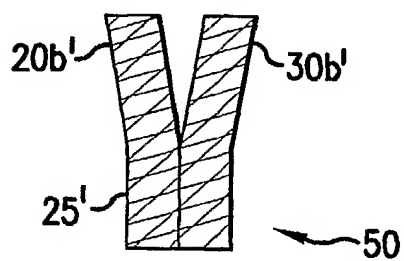


FIG. 5

4/11

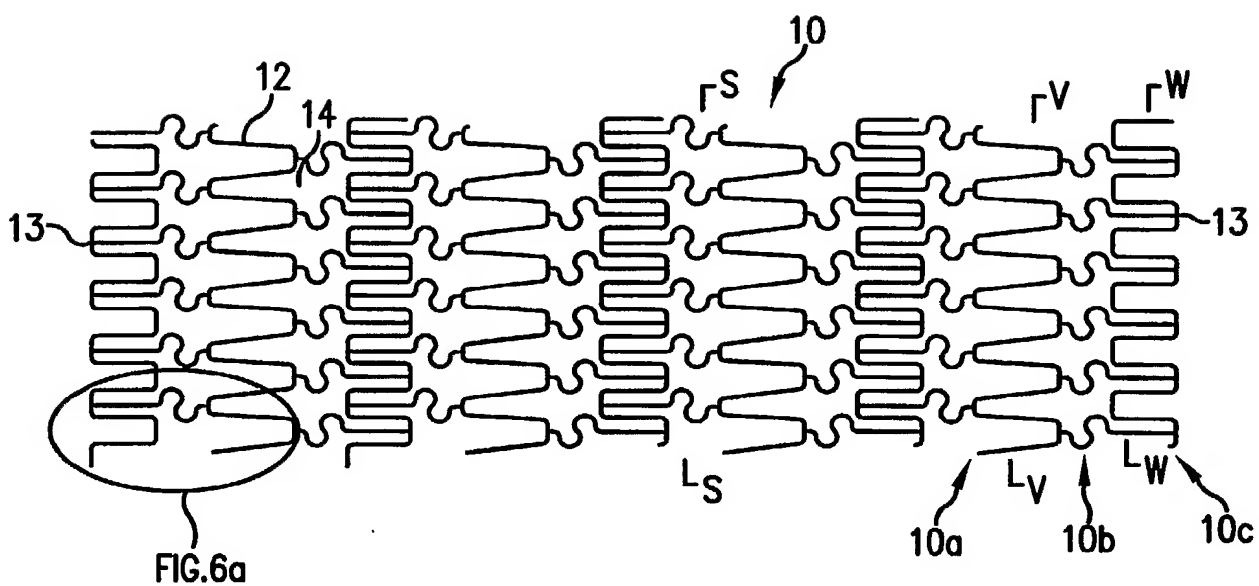


FIG. 6

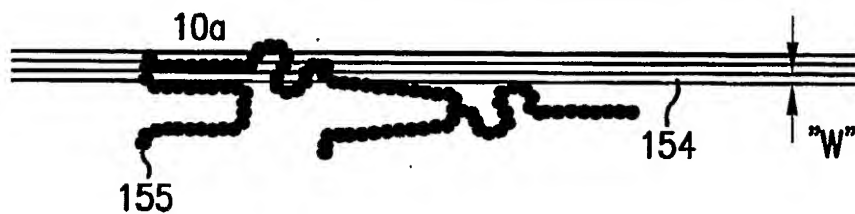


FIG. 6a

5/11

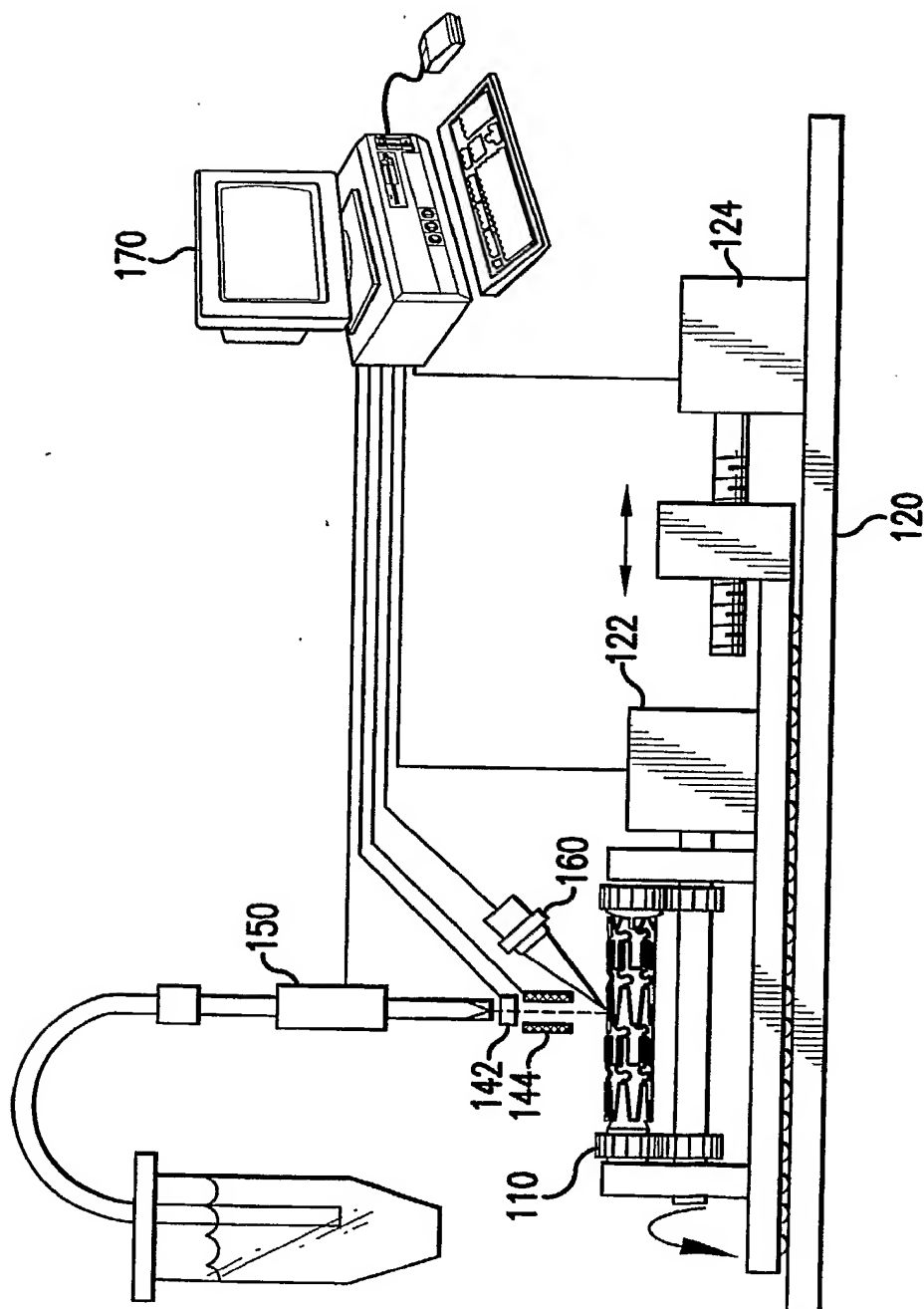


FIG. 7

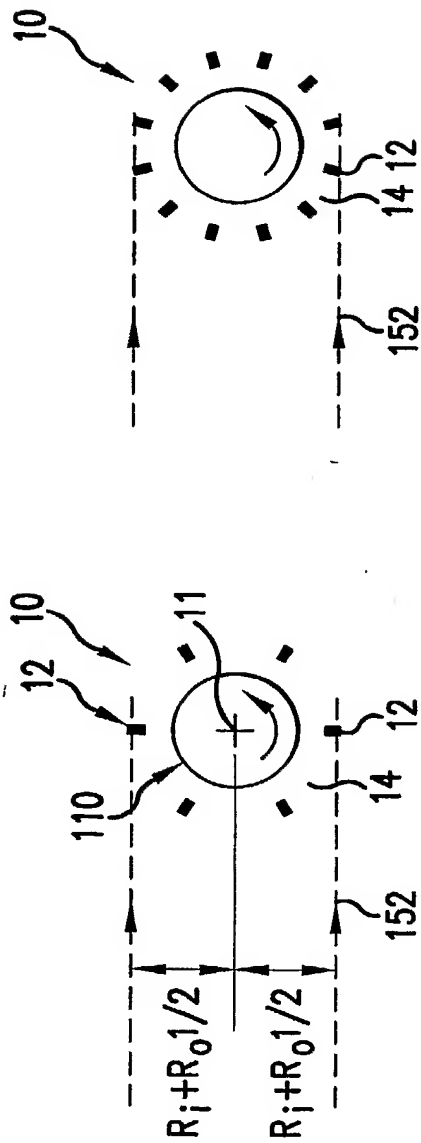


FIG. 8a

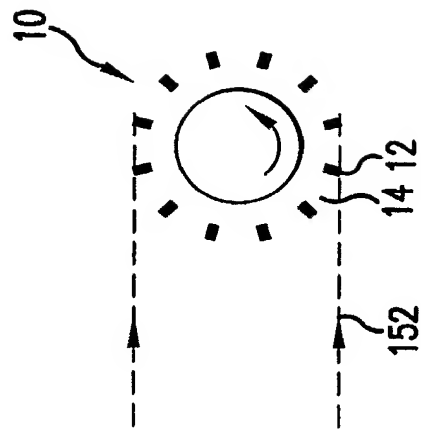


FIG. 8b

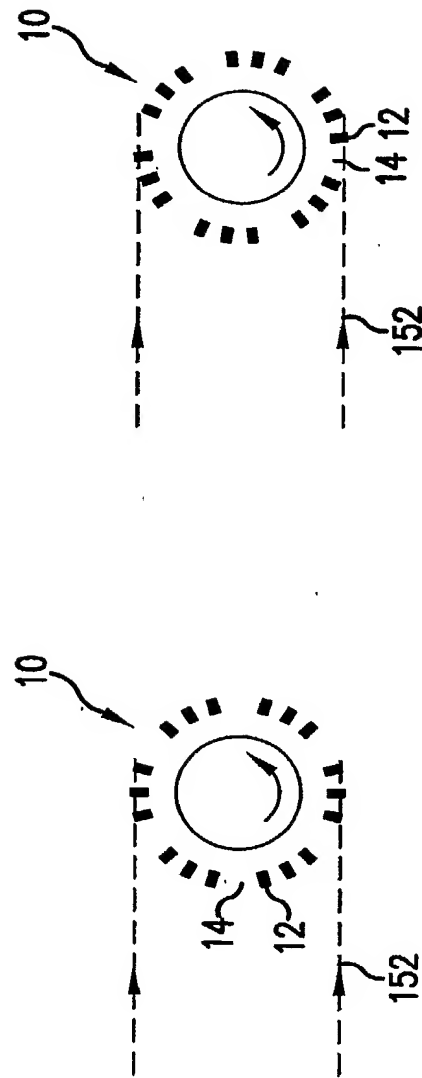


FIG. 8c

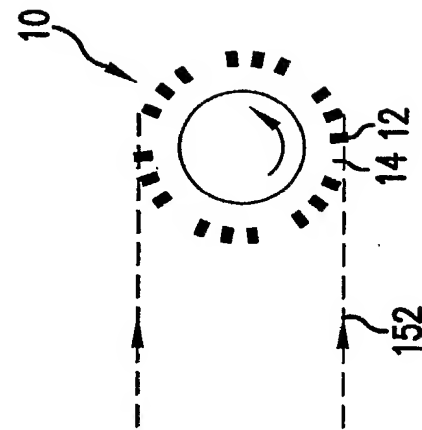


FIG. 8d

7/11

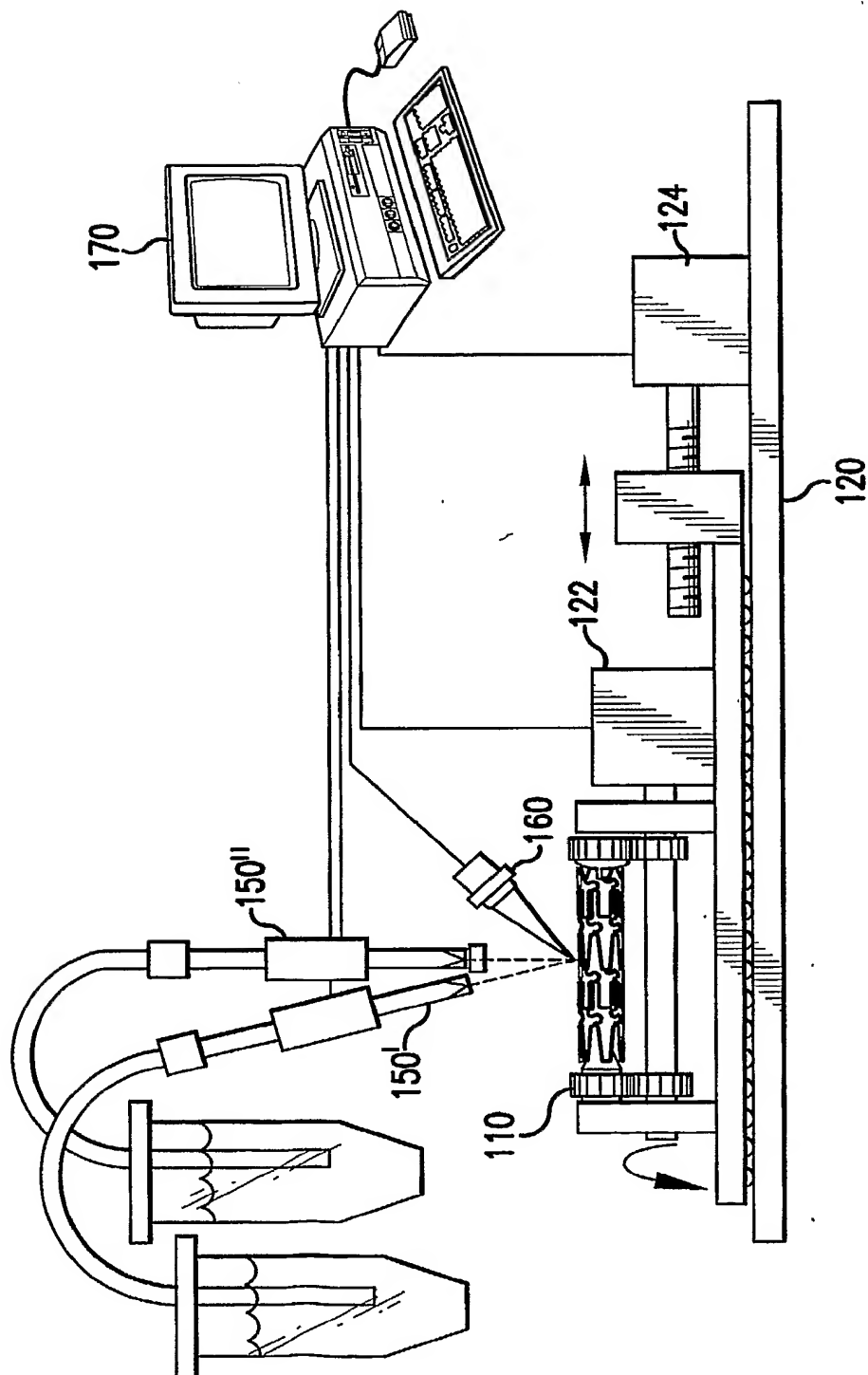


FIG. 9

8/11

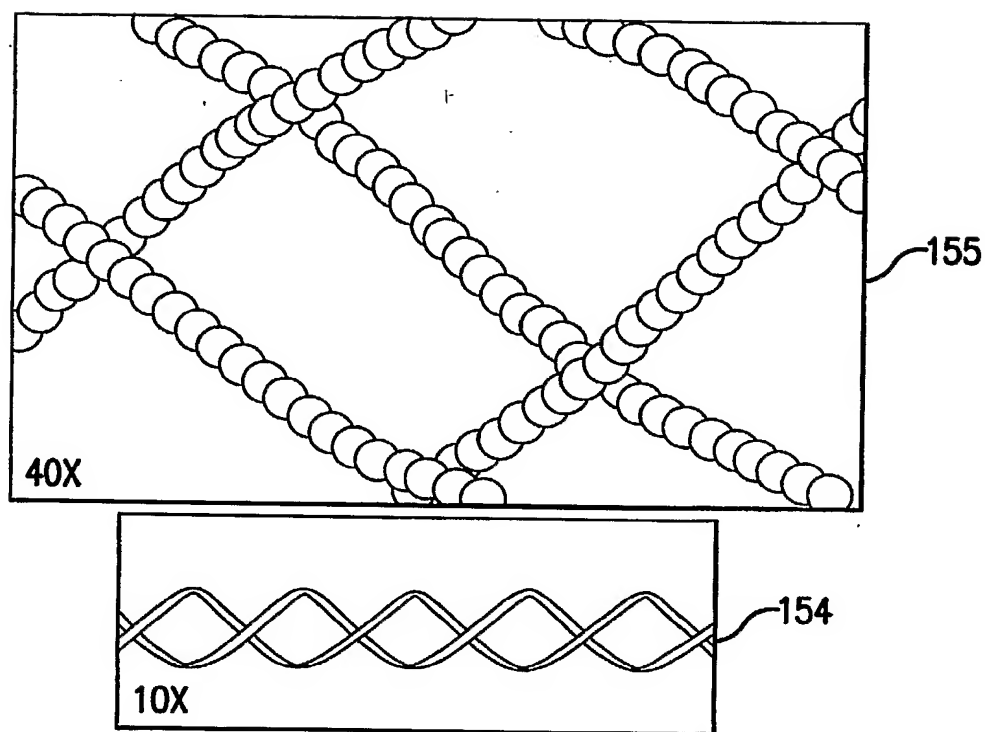


FIG. 10

9/11

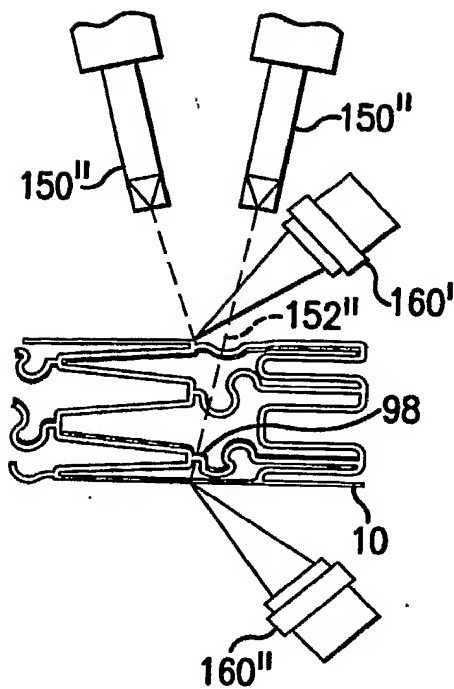


FIG. 11

10/11

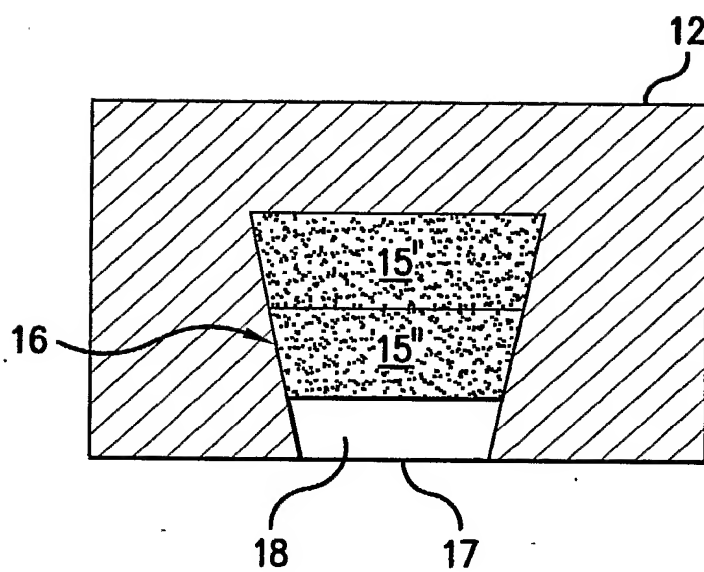


FIG. 12

11/11

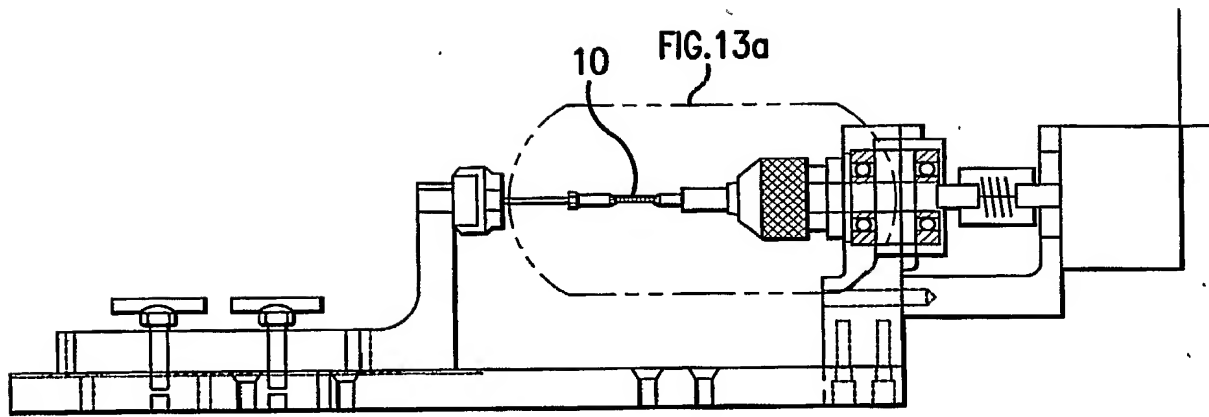


FIG. 13

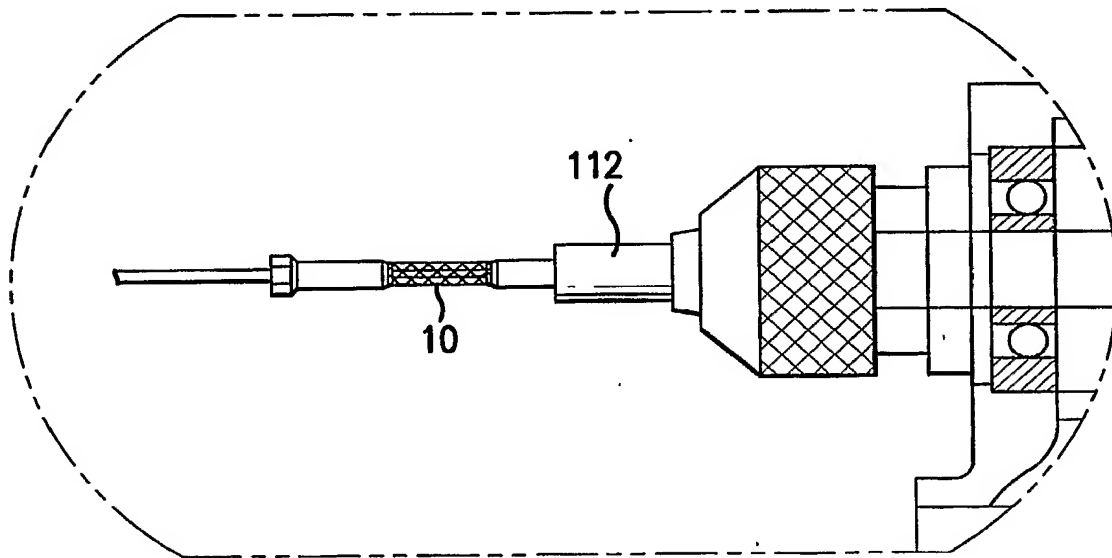


FIG. 13a

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/35627

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|----------------------------------|
| X | WO 01 91918 A (ADVANCED CARDIOVASCULAR SYSTEMS, INC.) 6 December 2001 (2001-12-06) the whole document | 1,5,7, 13, 15-18, 20-29 |
| A | EP 0 850 651 A (SCHNEIDER (USA) INC.) 1 July 1998 (1998-07-01) | |
| A | US 5 824 048 A (TUCH) 20 October 1998 (1998-10-20) | |
| A | WO 02 069848 A (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 12 September 2002 (2002-09-12) | |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

24 March 2004

Date of mailing of the international search report

31/03/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Smith, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/35627

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|---|--|
| WO 0191918 | A | 06-12-2001 | AU 6523801 A WO 0191918 A1 | 11-12-2001 06-12-2001 |
| EP 850651 | A | 01-07-1998 | CA 2225096 A1 EP 0850651 A2 JP 10192413 A US 5980972 A | 20-06-1998 01-07-1998 28-07-1998 09-11-1999 |
| US 5824048 | A | 20-10-1998 | US 5464650 A DE 9422438 U1 DE 69431457 D1 DE 69431457 T2 EP 1181943 A1 EP 0623354 A1 JP 8033718 A US 2002138048 A1 US 5837008 A US 5679400 A US 5624411 A US 5776184 A | 07-11-1995 25-04-2002 07-11-2002 26-06-2003 27-02-2002 09-11-1994 06-02-1996 26-09-2002 17-11-1998 21-10-1997 29-04-1997 07-07-1998 |
| WO 02069848 | A | 12-09-2002 | WO 02069848 A2 | 12-09-2002 |